PROCESS DEVELOPMENT AND OPTIMIZATION OF ZOLPIDEM TARTRATE TABLETS BY MOISTURE ACTIVATED DRY GRANULATION TECHNIQUE

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Submitted by

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MELMARUVATHUR - 603 319

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CERTIFICATE

This is to certify that the research work entitled "PROCESS DEVELOPMENT AND OPTIMIZATION OF ZOLPIDEM TARTRATE TABLETS BY MOISTURE ACTIVATED DRY GRANULATION TECHNIQUE" submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **NUSUM. SRINIVASA REDDY (Register No. 26106014)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2011-2012.

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CERTIFICATE

This is to certify that the dissertation entitled **"PROCESS DEVELOPMENT AND OPTIMIZATION OF ZOLPIDEM TARTRATE TABLETS BY MOISTURE ACTIVATED DRY GRANULATION TECHNIQUE"** the bonafide research work carried out by **NUSUM. SRINIVASA REDDY (Register No. 26106014)** in the Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under the guidance of **Mr. A. UMAR FARUKSHA,** M. Pharm., Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, during the academic year 2011-2012.

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NUSUM. SRINIVASA REEDY

Dedicated

To

My beloved parents...

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ABBREVIATIONS

API	----	Active pharmaceutical ingredient
MADG	----	Moisture activated dry granulation
UV	----	Ultra Violet
µg	----	Microgram
λ max	----	Absorption maximum
ml	----	Milli liter
mg	----	Milligram
nm	----	Nanometer
HPC	----	Hydroxypropyl Cellulose
HPMC	----	Hydroxypropyl Methyl Cellulose
Na CMC	----	Sodium Corboxy Methyl Cellulose
FTIR	----	Fourier Transform-Infra Red Spectroscopy
DSC	----	Differential Scanning Calorimetry
cm	----	Centimeter
%	----	Percentage
RH	----	Relative Humidity
USP	----	United States Pharmacopoeia
IP	----	Indian Pharmacopoeia
t	----	Time
ICH	----	International Conference on Harmonization

W/v	----	weight/volume
gm	----	Grams
RPM	----	Revolutions per Minute
mm	----	Millimeter
S. no	----	Serial Number
℃	----	Degree Celsius
min	----	Minutes
<	----	Less Than
>	----	More Than

INTRODUCTION...

1. INTRODUCTION

1. INTRODUCTION *(Leon Lachman, Hebert A. Lieberman, 1976)*

Active pharmaceutical compounds (drugs) are used for the treatment of a disease or for prophylactic purpose. An Active Pharmaceutical Ingredient (API) may exist in solid, liquid or semisolid form. They are rarely prescribed to the patients as such i.e. without adding excipients, since the desired effect may not be obtained. Earlier, it was thought that excipients are inert in nature but, in recent time it is well known that excipients can greatly modify the intended effect of a drug. The API and excipients are suitably processed in pharmaceutical industry to convert them into dosage forms such as tablet, capsule, suspension, solution, etc. The selection of excipients and processing of drug excipients mixture is as important as API itself.

Patient acceptability can be improved by controlling the organoleptic properties. Dosage form provides desired therapeutic level of a drug.

1.1 Tablet: *(Leon Lachman, Herbert A, Lieberman, 1991)*

It is a solid dosage form each containing a unit dose of one or more medicament/s. Tablets are solid, flat or biconvex discs prepared by compressing a drug or a mixture of drugs with or without suitable excipients. Tablets may be swallowed whole or being chewed. Some are dissolved or dispersed in water before administration. Some are put in oral cavity, where the active ingredient is liberated at a predetermined rate. Implants or passeries may also be presented in form of tablet.

Tablet may vary in shape and differ greatly in size and weight depending on the amount of medicinal substance and the intended mode of administration.

Properties:

The objective of the design and manufacture of the compressed tablet is to deliver orally the correct amount of drug in proper form, at or over the proper time and in desired location, and to have its chemical integrity protected to the point. So, the following properties are to be passed by the tablets:

- Should be an elegant product having its own identity while being free of defects such as chips, cracks, discoloration, contamination.
- Should have the strength to withstand the rigors of mechanical shocks encountered in its production, packaging, shipping, and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes over time.
- Must be able to release medicinal agents in the body in a predictable and reproducible manner.
- Must have a suitable chemical stability over time so as not to allow alteration of the medicinal agents.

Advantages: *(Aulton M.E, 2002)*

- Large scale manufacturing is feasible in comparison to other dosage forms. Therefore, economy can be achieved.
- Accuracy of dose is maintained since tablet is a solid unit dosage form.
- Tailor made release profile can be achieved.

- Longer expiry period and minimum microbial spillage owing to lower moisture content.
- As tablet is not a sterile dosage form, stringent environmental conditions are not required in the tablet department.
- Ease of packaging (blister or strip) and easy handling over liquid dosage form.
- Easy to transport in bulk. Emergency supply supplies can be carried by patients.
- Organoleptic properties (taste, appearance and odour) are best improved by coating of tablet.
- Product identification is easy and markings done with the help of grooved punches and printing with edible ink.
- Different types of tablets are available like buccal, floating, colon targeting, effervescent, dispersible, soluble, and chewable, etc.
- In comparison to parenterals dosage form, a doctor or a nurse is not required for administration. I.e. self administration is possible.

Disadvantages:

- It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
- Difficult to formulate a drug with poor wettability, slow dissolution into a tablet.
- Slow onset of action as compared to parenterals, liquid orals and capsules.
- The amount of liquid drug (e.g. Vitamin E, Simethicone) that can be trapped into a tablet is very less.
- Difficult to swallow for kids, terminally ill and geriatric patients.
- Patients undergoing radiotherapy cannot swallow tablets.

1.2 Types of tablets: *(Leon Lachman, Herbert A, Lieberman, 1976)*

With advancement in technology and increase in awareness towards modification in standard tablet to achieve better acceptability as well as bioavailability, newer and more efficient tablet dosage forms are being developed. The main reasons behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patient's perspective and utilize an approach that is unlikely to add complexity during regulatory approval process. To understand each dosage form, tablets here are classified by their route of administration and by the type of drug delivery system they represent within that route.

1.2.1 Oral tablets for ingestion:

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction.

A. Standard compressed tablets

B. Multiple compressed tablets

I. Compression coated tablet

II. Layered tablet

III. Inlay tablet

C. Modified Release tablet

D. Delayed action tablet

E. Targeted tablet

I. Floating tablets

II. Colon targeting tablets

F. Chewable Tablets

G. Dispersible Tablets

1.2.2 Tablets used in the Oral cavity:

The tablets under this group are aimed release API in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity.

A. Lozenges and troches

B. Sublingual tablet

C. Buccal tablet

D. Dental cones

E. Mouth dissolved tablet

1.2.3 Tablets administered by other routes:

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. These tablets may be

inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application.

A. Vaginal tablet

B. Implants

1.2.4 Tablets used to prepare solution:

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used.

A. Effervescent tablet

B. Hypodermic tablet

C. Soluble tablet

1.3 Ideal properties of API for formulating tablet:

- High Purity
- High stability
- Good compatibility with excipients
- Optimum bulk powder properties
- Optimum and Uniform particle size-particle size distribution
- Spherical shape
- Good flowability
- Optimum moisture content
- Good compressibility
- Absence of static charge on surface

- Good organoleptic properties

1.4 Excipients: *(Dr. P. K. Sahoo)*

Conventional oral tablets for ingestion usually contain some classes of components in addition to active ingredients. They are:

Diluents:

Diluents are fillers designed to make up the required bulk of the tablet when the drug dosage itself is inadequate to produce this bulk. The dose of some drugs is sufficiently high that no filler is required. Eg: Lactose, Starch, Dextrose, Mannitol, Sorbitol, Sucrose, Microcrystalline cellulose (Avicel).

Binders and adhesives:

These materials are added either dry or in liquid form during wet granulation to form granules or to promote cohesive compacts for directly compressed tablets.

Eg: Acacia, Tragacanth, Gelatine, Starch, Alginates and cellulose derivatives.

Disintegrates:

A disintegrant is added to most tablet formulations to facilitate a breakup or disintegration of the tablet when it contacts water in the gastrointestinal tract. Disintegrates may function by drawing water into the tablet, swelling, and causing the tablet to burst apart. Such tablet fragmentation may be critical to the subsequent dissolution of the drug and to the attainment of satisfactory drug bioavailability.

Eg: Starch, Veegum, Bentonite, Sodium carboxy methylcellulose.

Lubricants, Anti-adherents, and Glidants:

These three classes of materials are typically described together because they have overlapping functions. A material that is primarily described as an anti-adherent is

typically also a lubricant, with some glidant properties as well. The differentiation between these terms is as follow: Lubricants are intended to reduce the friction during tablet ejection between the walls of the tablet and the walls of the die cavity on which the tablet was formed. Anti adherents has the purpose of reducing sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall Glidants are intended to promote the flow of the tablet granulation or powder materials by reducing friction between the particles.

Eg: Talc, Calcium stearate and Starch.

Colours, flavours and sweeteners:

The use of colours and dyes in tablet making has three purposes over the years: disguising of off-colours drugs, product identification, and production of a more elegant decertification of many synthetic dyes. The availability of natural vegetable colors is limited, and these colors are often unstable. Two forms of colors have typically been used in tablet preparation. These are the FD&C and D&C dyes.

Flavours are usually limited to chewable tablets or other tablets intended to dissolve in the mouth. The use of sweeteners is primarily limited to chewable tablets to exclude or limit the use of sugar in the tablets.eg: Saccharin, Aspartame.

1.5 Method of tablet preparation: (*Leon Lachman, Herbert A, Lieberman, 1976*)

There are three general methods of tablet preparation.

A. Direct compression method

B. Granulation method

i. Dry granulation method

ii. Wet granulation method

A. Direct compression method:

The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pre-treatment of the powder blend by wet or dry granulation procedure is required.

Manufacturing steps for direct compression:

Direct compression involves comparatively few steps:

i) Milling of drug and excipients.

ii) Mixing of drug and excipients.

iii) Tablet compression

Direct compression excipients mainly include diluents, binders and disintegrants. Generally these are common materials that have been modified during the chemical manufacturing process, in such a way to improve compressibility and flowability of the material. The physicochemical properties of the ingredients such as particle size, flowability and moisture are critical in direct compression tableting. The success of direct compression formulation is highly dependent on functional behaviour of excipients.

B. Granulation method:

Granulation may be defined as a size enlargement process which converts small particles into physically stronger & larger agglomerates.

Granulation method can be broadly classified into three types: Wet granulation, Dry granulation, and Dry Granulation incorporating bound moisture.

Ideal characteristics of granules:

The ideal characteristics of granules include uniformity, good flow, and compatibility. These are usually accomplished through creation of increased density, spherical shape, narrow particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), and incorporation of binder, if necessary.

The effectiveness of granulation depends on the following properties

i) Particle size of the drug and excipients

ii) Type of binder (strong or weak)

iii) Volume of binder (less or more)

iv) Wet massing time (less or more)

v) Amount of shear applied to distribute drug, to the binder and moisture.

vi) Drying rate (Hydrate formation and polymorphism)

B.I Wet granulation:

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying.

Steps involved in the wet granulation:

i) Mixing of the drugs and excipients

ii) Preparation of binder solution

iii) Mixing of binder solution with powder mixture to form wet mass.

iv) Coarse screening of wet mass using a suitable sieve (6-12 screens)

v) Drying of moist granules.

vi) Screening of dry granules through a suitable sieve (14-20 screens)

vii) Mixing of screened granules with disintegrant, glidant, and lubricant.

Special wet granulation techniques:

i) High shear mixture granulation

ii) Fluid bed granulation

iii) Extrusion-spheronization

iv) Spray drying

B.II Dry granulation:

In dry granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is precompressed and the resulting tablet or slug are milled to yield the granules. The other method is to precompress the powder with pressure rolls using a machine such as Chilosonator.

Steps involved in the dry granulation:

i) Milling of drugs and excipients

ii) Mixing of milled powders

iii) Compression into large, hard tablets to make slug

iv) Screening of slugs

v) Mixing with lubricant and disintegrating agent.

Advanced Granulation Techniques: *(Ismat U, 2011)*

Over a period of time, due to technological advancements and in an urge to improve commercial output various newer granulation technologies have been evolved such as

1. Steam Granulation
2. Melt/Thermoplastic Granulation
3. Moisture Activated Dry Granulation (MADG)
4. Moist Granulation Technique (MGT)
5. Thermal Adhesion Granulation Process (TAGP)
6. Foam Granulation

1. Steam Granulation:

Pure steam is a transparent gas. At standard temperature and pressure, pure steam (unmixed with air, but in equilibrium with liquid water) occupies about 1,600 times the volume of an equal mass of liquid water

This process is simply a modification of conventional wet granulation method. Here steam is used as a binder instead of water. Process offers several advantages and disadvantages over other conventional granulation methods such as

Advantages:

1. Uniformly distributed in the powder particles
2. Higher diffusion rate
3. Results in more spherical granule formation
4. Thermally aids in drying process
5. Higher dissolution rate of granules because of larger surface area generated
6. Time efficient
7. Environment friendly
8. No health hazards to operator
9. Regulatory compliance
10. Maintain sterility

Disadvantages:

1. Requires special equipment for steam generation and transportation
2. Requires high energy inputs.
3. Thermo labile materials are poor candidates
4. More safety measure required
5. Not suitable for all the binders.

2. Melt Granulation:

Melt Granulation process has been widely used in the pharmaceutical industry for the preparation of both immediate and controlled release formulations such as pellets, granules, and tablets. This process has also been widely accepted for the enhancement of dissolution profile and bioavailability of poorly water soluble drugs by forming solid dispersion.

Melt Granulation is also known as "Thermoplastic Granulation" as the granulation is achieved by adding a meltable binder which is in solid state at room temperature but preferably melts in the temperature range of $50^{oC} – 80^{oC}$ [20]. No further addition of liquid binder or water is required in the process as the binder in the melted state itself act as granulating liquid and dried granules can be easily obtained by simple cooling at room temperature. This process offers various advantages such as-

Advantages:

1. Time and cost effective, as it eliminates the liquid addition and drying steps.
2. Water sensitive drugs are good candidates.
3. Controlling and modifying the release of drugs.
4. Regulatory compliance.

Disadvantages:

1. Heat sensitive materials are poor candidates.
2. Binders having melting point in the specific range can only be utilized in the process.

3. Moisture Activated Dry Granulation (MADG):

MADG is a process in which moisture is used to activate granule formation, without the need to apply heat to dry the granules.

There are two main stages in MADG:

1. Agglomeration
2. Moisture distribution/ Absorption

During agglomeration, drug is blended with diluents(s) and binder in the powder form, to obtain a uniform mixture. This blend constitutes approximately 50-80% of

formula weight. While mixing, a small amount of water (1-4%) is sprayed as small droplets onto the powder blend, which moistens the binder and makes it tacky. The binder facilitates the binding of the drug and excipients as they move in a circular motion forced by the mixer blades. The process does not results in larger lumps formation as the amount of water used in this process is very small as compared to the other conventional wet granulation techniques. The particle size of the agglomerates generally falls in the range of 150–500 μm. In moisture distribution/absorption, moisture absorbents, such as microcrystalline cellulose or silicon dioxide, are added while mixing continues. When they come into contact, the moisture absorbents pick up moisture from the moist agglomerates, resulting in moisture redistribution within the mixture. When this happens, the entire mixture becomes relatively dry. While some of the moisture is removed from the wet agglomerates, some of these agglomerates remain almost intact and some usually the larger particles may break up. This process results in granulation with more uniform particle size distribution.

Advantages:

1. Applicable to more than 90% of the granulation need for pharmaceutical, food and nutritional industry.
2. Time efficient
3. Very few variables involved in the process.
4. Suitable for continuous processing
5. Less energy involved during processing.

Disadvantages:

1. Moisture sensitive and high moisture absorbing API is poor candidates.

2. Formulations with high drug loading are difficult to develop.

4. Moist Granulation Technique (MGT):

MGT works on the same principle as Moisture Activated Dry Granulation (MADG) described earlier. It involves binder activation by adding a minimum amount of liquid. Then, excess of moisture present in the blend is removed by adding moisture absorbing material like Microcrystalline Cellulose (MCC) which eliminates the drying step. It is applicable for developing a controlled release formulation.

5. Thermal Adhesion Granulation Process (TAGP):

TAGP involves granulation by adding very less amount of water or solvent as compared to the traditional wet granulation methods. In this process drug and excipient mixture heated at a temperature range from 30oC to about 130oC in a closed system under mixing by tumble rotation until the formation of granules take place. Drying step is not required in most instances due to low amount of moisture added in the process. Granules of required particles size can be obtained after cooling and screening. It provides granules with good flow properties and binding capacity to form tablets of low friability, adequate hardness and have a high uptake capacity for active substances whose tableting is poor.

6. Foam Granulation:

Foam granulation technique involves addition of liquid binders as aqueous foam. The advantage of foamed binder addition conventional binder addition method includes:

1. No spray nozzle is used
2. Improve process robustness
3. Less water required for granulation

4. Time efficient drying

5. Cost effective

6. Uniform distribution of binder

7. No over wetting

8. Applicable for water sensitive formulation

1.6 Tablet compression: *(Mudbidri A, 2010)*

After the preparation of granules (in case of wet granulation) or sized slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to get final product. The compression is done either by single punch machine (stamping press) or by multi station machine (rotary press).

The tablet press is a high-speed mechanical device. It 'squeezes' the ingredients into the required tablet shape with extreme precision. It can make the tablet in many shapes, although they are usually round or oval. Also, it can press the name of the manufacturer or the product into the top of the tablet.

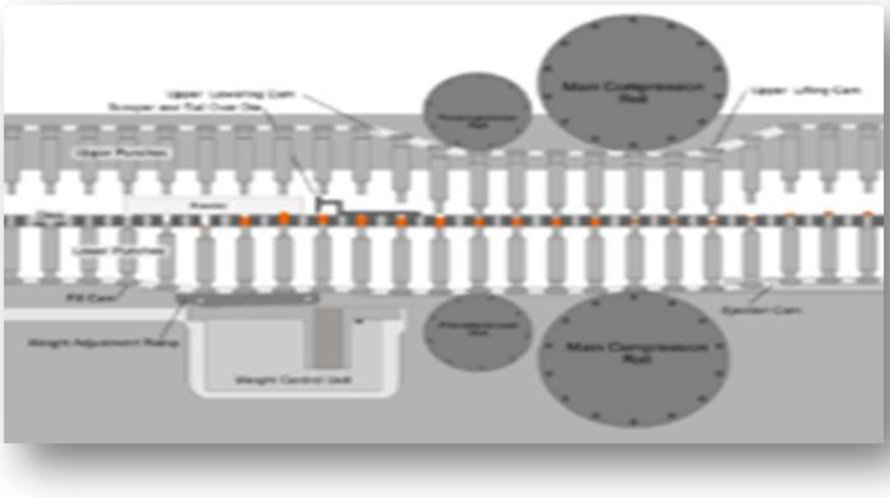


Figure 1.1: Punches arrangement of tablet compression machine

Each tablet is made by pressing the granules inside a die, made up of hardened steel. The die is a disc shape with a hole cut through its centre. The powder is compressed in the centre of the die by two hardened steel punches that fit into the top and bottom of the die.

The punches and dies are fixed to a turret that spins round. As it spins, the punches are driven together by two fixed cams - an upper cam and lower cam. The top of the upper punch (the punch head) sits on the upper cam edge .The bottom of the lower punch sits on the lower cam edge.

The shapes of the two cams determine the sequence of movements of the two punches. This sequence is repeated over and over because the turret is spinning round.

The force exerted on the ingredients in the dies is very carefully controlled. This ensures that each tablet is perfectly formed. Because of the high speeds, they need very sophisticated lubrication systems. The lubricating oil is recycled and filtered to ensure a continuous supply.

Figure 1.2: Tablet Compression machine

Common stages occurring during compression:

Stage 1: Upper punch is withdrawn from the die by the upper cam. Lower punch is low in the die so powder falls in through the hole and fills the die.

Stage 2*:* Lower punch moves up to adjust the powder weight-it raises and expels some powder

Stage 3*:* Upper punch is driven into the die by upper cam Lower punch is raised by lower cam. Both punch heads pass between heavy rollers to compress the powder.

Stage 4*:* Upper punch is withdrawn by the upper cam. Lower punch is pushed up and expels the tablet. Tablet is removed from the die surface by surface plate

Stage 5*:* Return to stage 1.

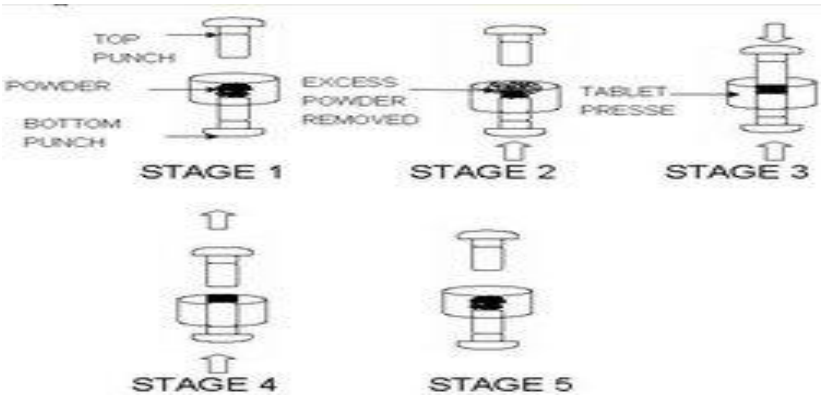


Figure 1.3: Stages occurring during compression

Coating:

Coated tablets are defined as "tablets covered with one or more layers of mixture of various substances such as natural or synthetic resins, gums, inactive and insoluble filler, sugar, plasticizer, polyhydric alcohol ,waxes ,authorized coloring material and sometimes flavouring material. Coating may also contain active ingredient. Substances used for coating are usually applied as solution or suspension under conditions where vehicle evaporates.

1.7 Tablets problems and how to overcome:

An ideal tablet should be free from any visual defect or functional defect. The advancements and innovations in tablet manufacture have not decreased the problems, often encountered in the production, instead have increased the problems, mainly because of the complexities of tablet presses; and/or the greater demands of quality.

Here, we will discuss the imperfections found in tablets along–with their causes and related remedies. The imperfections are known as: 'VISUAL DEFECTS' and they are either related to imperfections in any one or more of the following factors:

I. Tableting Process

II. Excipients

III. Machine

The defects related to tableting process are as follows:

i) Capping: It is partial or complete separation of the top or bottom of tablet due air-entrapment in the granular material.

ii) Lamination: It is separation of tablet into two or more layers due to air-entrapment in the granular material.

iii) Cracking: It is due to rapid expansion of tablets when deep concave punches are used.

The defects related to Excipient are as follows:

iv) Chipping: It is due to very dry granules.

v) Sticking: It is the adhesion of granulation material to the die wall

vi) Picking: It is the removal of material from the surface of tablet and its adherence to the face of punch.

vii) Binding: These problems (v, vi, vii) are due to more amount of binder in the granules or wet granules.

The defect related to more than one factor:

viii) Mottling: It is either due to any one or more of these factors: Due to a coloured drug, which has different colour than the rest of the granular material? (Excipient- related); improper mixing of granular material (Process-related); dirt in the granular material or on punch faces; oil spots by using oily lubricant.

The defect related to Machine:

ix) Double impression: It is due to free rotation of the punches, which have some engraving on the punch faces.

Further, in this section, each problem is described along-with its causes and remedies which may be related to either of formulation (granulation) or of machine (dies, punches and entire tablet press).

Table 1.1: Tablet trouble shooting *(Leon Lachman, Herbert A, Lieberman, 1991)*

PROBLEMS	CAUSES	REMEDY
CAPPING LAMINATION	• Granulation too dry • Compression too hard • Damaged upper punchers • Machine too fast • Excessive lubrication • Less binder in granules • Air present in granules which cannot escape while compression	• Increase moisture content • Reduce compression pressure • Replace the tools which are damaged • Reduce machine speed reduce or change the lubrication • Increase binder • Improve granulation • Use tapered dies
CHIPPING	• Damaged punches or dies • Compression too fast • Faulty machine setting • Less binder	• Replace the damage punches or dies • Reduce the compression speed • Proper machine setting • Increase binder

COLLER FORMATION	• Too much fines	• Reduce fines
BLACK MARKS ON TABLETS	• Improper feed frame setting • Excessive Moisture • Oversized granules • Granules having black particles prior to compression • Lubricants Greece or oil may be contaminating the powder	• Improve feed frame setting • Avoid excess moisture • Reduce granule size • Avoid contamination with Greece or oil
DISSOLUTION	• Large granules • Tables too hard • Excess lubrication	• Reduce granules size • Reduce tablet hardness • Reduce compression hardness

1.8 OPTIMIZATION:

Optimization can be defined as choosing the best element from some set of available alternatives. In Pharmacy, word "Optimization" is found in the literature referring to any study of formula. In development projects, pharmacists generally experiment by a series of logical steps, carefully controlling the variables and changing one at a time until satisfactory results are obtained. This is how the optimization is done in pharmaceutical industry.

1.8.1 Process optimization:

This involves optimization of process parameters during the manufacturing process.

1.8.2 Granulation optimization:

The process of granulation is optimized with adjusting granulation control parameters like:

- Granulation time
- Speed of choppers of mixer blades
- Solvent addition rate and overall amount
- Ratio of intra granular disintegrant and binder agent
- Screen size of milling
- Adjusting mill screen size up or down to fine tune hardness
- Evaluation of optimized granulate and tablet attributes
- Fluid bed drying temperature versus target LOD and range limits and their effect on granulate and tablet properties.

1.8.2 Blending optimization:

While blending, the following parameters are to be considered.

- Blending time
- Pre-blending and final blending
- The effect on content uniformity, granule lubrication and dissolution profile
- Evaluation of unit dose sampling versus content uniformity.

1.8.3 Compression optimization:

While compression optimization, following parameters are to be considered -

- Evaluation of compression machine RPM and it's effect on tablet properties (weight variation)
- Effect of hardness on tablet properties (aging, dissolution, friability)
- Evaluation of hardness range limits
- Evaluation of stability results on the basis of optimized manufacturing process.

1.9 MOISTURE ACTIVATED DRY GRANULATION (MADG): *(Ismat U, 2009)*

As the name implies, this is a process where moisture is used to activate the granule formulation, but the granules are not heat dried.

MADG is a simple, economical, clean, lean and robust process that creates granulation with very good physical properties and finished products with satisfactory quality attributes. It is applicable to many of the pharmaceutical industry's granulation needs for solid dosage form development and can be described as a 'one-pot' granulation process.

MADG is a very simple and innovative process where granules are created with water and a granulating binder, as in wet granulation, but are not heat dried or milled. This process helps to minimize endpoint sensitivity.

Moisture Activated Dry Granulation (MADG) was developed in response to the difficulties experienced with wet granulation, in terms of endpoint, drying and milling. Wet granulation process endpoint is very sensitive to granulation time and shear. The wet granules need to be dried to a narrow range of moisture contents, which is difficult. The dried granules need to be milled, but the milled granules often have either too many fines or too many coarse particles (or both) - an undesirable bimodal distribution.

In 1987, Ullah et al., published a paper about a simple and novel granulation process called moisture-activated dry granulation (MADG). In this granulation process, a small amount of water is used to activate the granule formation (i.e., perform agglomeration) without requiring hot air drying of the granules. After creating the moist agglomerates, this process uses stepwise addition and blending of common pharmaceutical ingredients that absorb and distribute moisture, thus resulting in a uniform, free-flowing, and compatible granulation.

In 1990, Chen et al., published a study comparing the MADG process with the conventional granulation processes for sematilide hydrochloride tablets. Although the active pharmaceutical ingredient (API) in the formulation was cohesive and fluffy, the granulation made with the MADG process was generally comparable with that made through the wet-granulation and roller-compaction processes.

In addition, the authors found that MADG was not only a shorter process, but that the final granulation made with the MADG process showed superior

flowability and better tablet-content uniformity. In 1994, Christensen employed the MADG process to successfully make pharmaceutical granulations with micro crystalline cellulose, potato starch, and both of these excipients. MADG also offers energy savings, a short manufacturing time, and fewer critical formulation and process variables, which makes it an easier candidate than conventional wet or dry granulation processes with which to implement the FDA's Quality by Design concepts.

1.9.1 The MADG process:

The Moisture Activated Dry Granulation involves two major stages

Agglomeration

Moisture distribution And Absorption Stage

Success depends on the selection and order in which the formulation ingredients are added, as well as how the process is carried out. Figure shows a flow diagram of the MADG process.

Moisture-Activated Dry Granulation--Formulation Development:

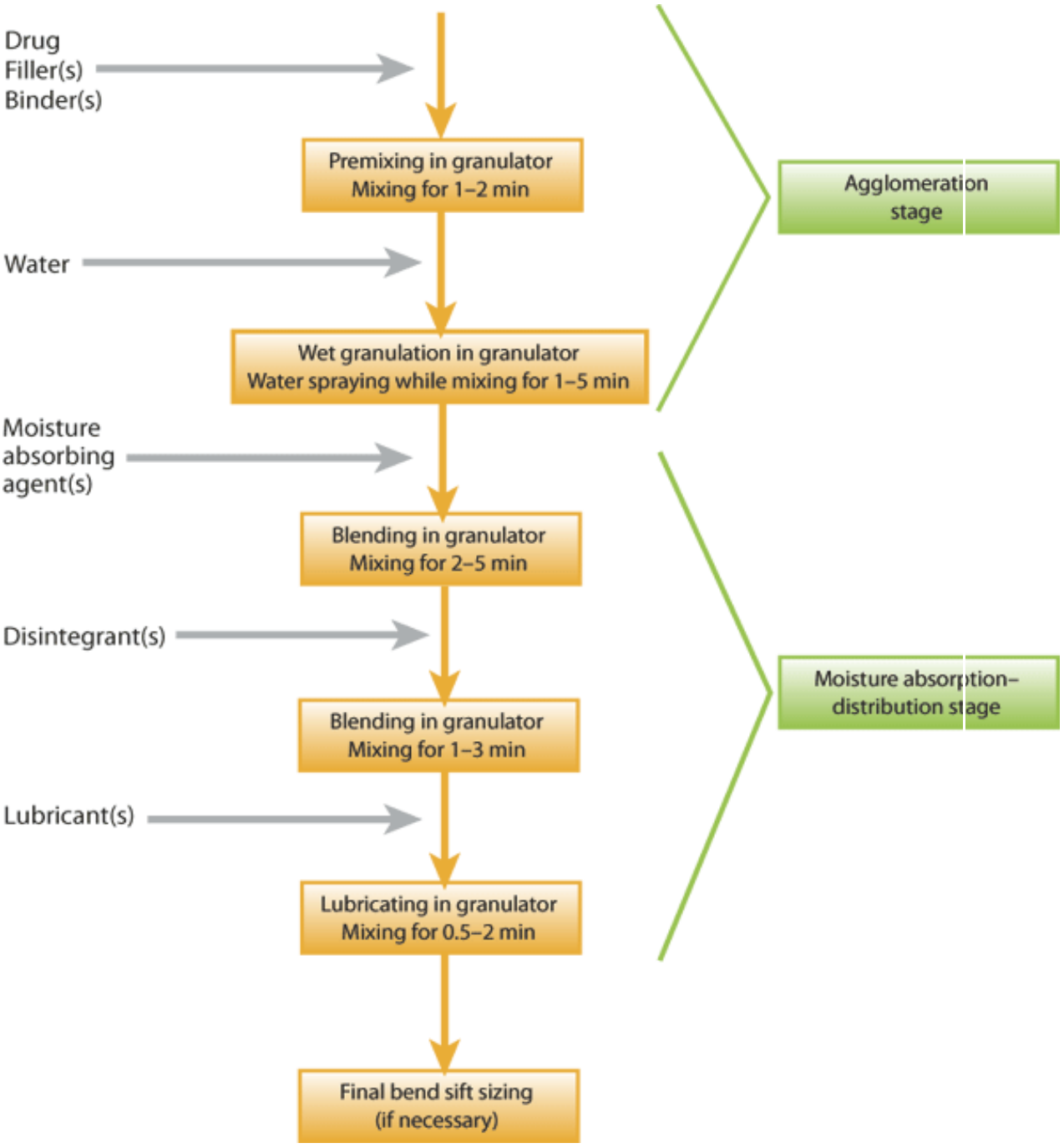


Figure 1.4: Flow diagram of the moisture-activated dry-granulation process

1.9.1.1 Agglomeration:

In this stage, all or part of the drug is mixed with filler(s) and an agglomerating binder to obtain a uniform mixture. During mixing, a small amount of water (1–4%) is sprayed onto the powder blend; water droplets hydrate the dry binder and create tacky nuclei or tacky wet mass. The binder functions as the drug and excipients move in the circular motion caused by the mixer impellers or blades. Dry powder particles adhere to the wet nuclei or wet tacky mass to create moist agglomerates. The resulting agglomerates are small and spherical because the amount of water used in the MADG process is much lower than that in conventional wet granulation. The agglomerates therefore cannot grow into large, wet lumps. The particle size of the agglomerates generally is in the range of 150–500 μm. It is possible, based on the drug loading technique, to add only part of the drug to the formulation during the agglomeration stage. The remaining drug can be added after the moist agglomerates have been formed. The added drug particles adhere to the wet agglomerates and become incorporated into them. The process does not create large granules, which would need milling, and because very little water is used in the process, the endpoint is not sensitive to blending.

1.9.1.2 Moisture-Distribution and Absorption Stage:

In this stage, moisture absorbents such as microcrystalline cellulose or silicon dioxide are added as mixing continues. When these agents come into contact with the moist agglomerates, they pick up moisture from the agglomerates and redistribute moisture within the mixture. The entire mixture thus becomes relatively dry. Although

some of the moisture is removed from the wet agglomerates, some of these agglomerates remain almost intact, and some, usually the larger particles, may break up. This process results in a granulation with uniform particle-size distribution. The process continues with the addition of a disintegrant to the mixture, followed by blending for a few minutes. Then, during mixing, lubricant is added and blended for sufficient time to achieve adequate lubrication this step completes the MADG granulation process. Excluding material loading, the actual processing time for the MADG process is only 10–20 min. Even for a commercial-scale batch, the processing time is essentially the same as it would be for a laboratory- or pilot-scale batch. Beginning with the premixing of the drug and excipients, the final granulation could be ready for tablet compression, encapsulation, or powder filling in about an hour.

Advantages:

Applicable to more than 90% of the granulation needs for pharmaceutical, food and nutritional industry

- Short processing time
- Very few variables, resulting in less need for expensive PAT technology
- Applicable to a number of formulations, including high and low drug load formulations, polymer matrix type controlled release formulations, and soluble and insoluble drug formulations
- Suitable for continuous processing
- It uses very little energy, so it is a green process.
- Reproducible and scalable.

Disadvantages:

- ❖ Moisture sensitive and high moisture absorbing APIs are poor candidates.
- ❖ Formulations with high drug loading are difficult to develop.
- ❖ Could be other issues with the API, with high-drug load formulations being particularly difficult to develop
- ❖ Less familiarity with the process and some apprehension towards adoption.

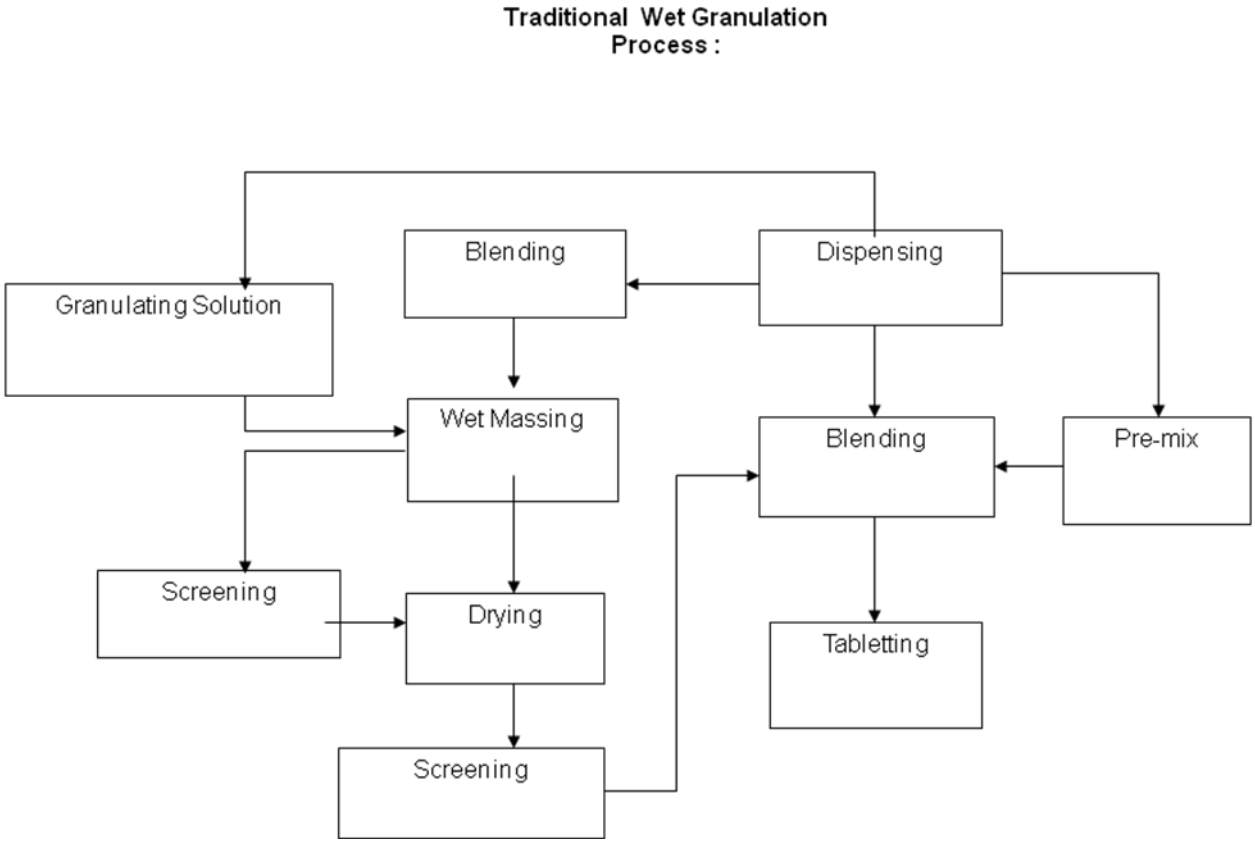


Figure 1.5: Traditional wet granulation process

MADG process:

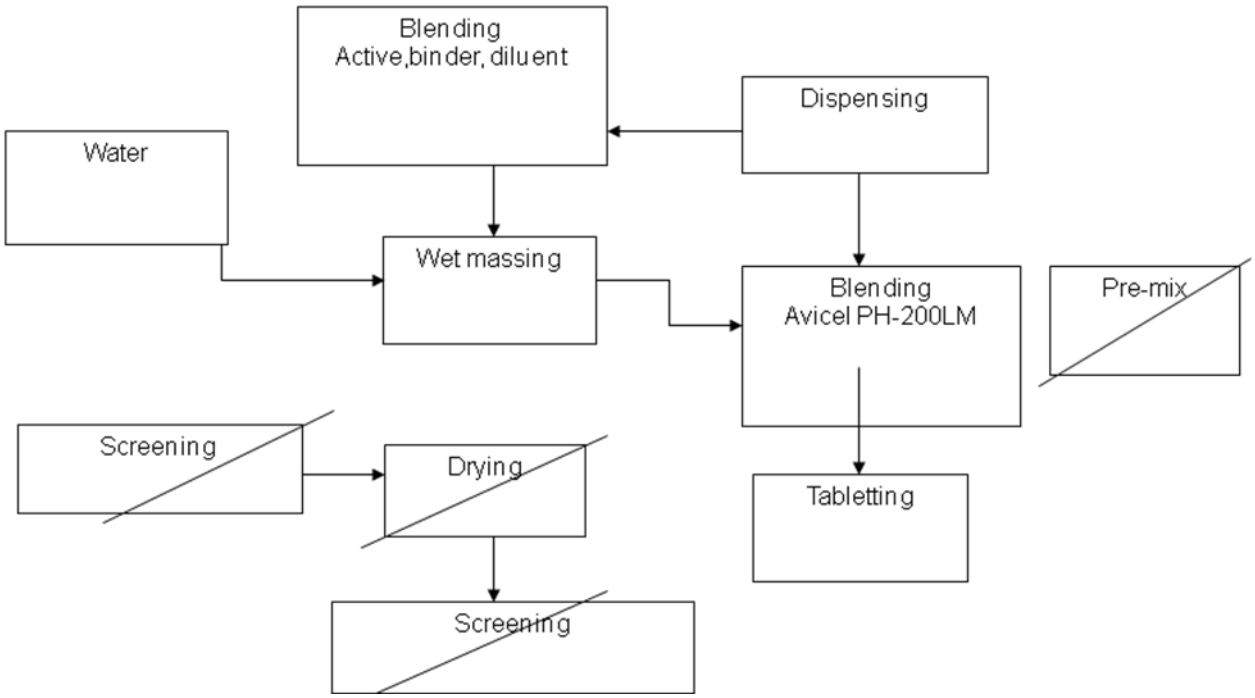


Figure 1.6: Moisture-activated dry-granulation process:

Table 1.2: MADG vs WG and primary and secondary benefit's over wet granulation

MADG VS WG	PRIMARY BENEFIT	SECONDARY BENEFIT
Lower amount of added moisture (4%to 8% total)	No drying	Faster process, increased efficiencies, lower production costs.
Single production equipment(high shear granulator)	Lower investments and maintenance.	Increased efficiencies, lower production costs
No equipment change	Reduces process time	Lower production costs. Faster product development, faster to market.
No milling required	No fines	Higher yields, lower costs
Lower tablet capping (low moist)	Lower tablet rejection rate	Higher yields, lower costs
No over or under granulation	Fewer scrapped batches	Higher asset utilization, lower costs

1.9.1.3 MADG Formulation development:

Assessment of API Wettability:

Drug solubility, particle-size distribution, and desired drug loading in the formulation are the primary factors to be considered for an MADG-based development. In general, a great amount of agglomerating binder and water are needed to create the agglomerates when a high drug load is desired for a drug with low solubility and small particle size. The converse is also true. Less agglomerating binder and water is required if the drug is water-soluble, the particle size is not small (e.g., > 10 μm), and the drug loading is low (e.g., < 25%). Self-granulating drugs sometimes do not require any binder and need less water to granulate. Drug attributes such as wettability and agglomeration characteristics should be determined experimentally if they are not already known. Scientists can add water to the drug in a vial or in a small beaker using a syringe and stir the mixture with a small spatula. Generally, the drug is a suitable candidate for an MADG process if it can be wetted with 1–2% of water. If, on the other hand, the drug does not easily wet with 1–2% water, the formulation likely needs more binding material and water. Therefore, the higher the percentage of water needed to wet the drug, the more water or binder is needed for the agglomeration stage. As previously mentioned, it is difficult to develop an MADG process if a high amount of water or binder is required for the formulation.

1.9.2 Excipients for the MADG process: *(Ismat U, Jennifer W, 2009)*

1.9.2.1 Fillers for the MADG process during agglomeration:

It is critical to select suitable excipients for a successful MADG process. Unlike the conventional wet-granulation process, which often employs microcrystalline cellulose or starch as fillers, MADG process uses nonabsorbent, easy-to-wet fillers such as lactose monohydrate and mannitol. The main reason for this selection is that microcrystalline cellulose and starch-based excipients absorb and retain a considerable amount of moisture during agglomeration. Because of this characteristic, more than the desired amount of water must be used during processing to form proper wet agglomerates. To ensure proper agglomeration, filler particles must not be too coarse or too fine. In general, coarse particles do not agglomerate easily, and fine particles require more moisture for agglomeration.

In rare cases, the drug itself could be soluble and become tacky upon moistening. Such drugs are classified as self-granulating. For these types of drugs, it is beneficial to include moisture absorbents during the agglomeration stage if a high drug-load formulation is desired in the MADG. Microcrystalline cellulose or starch products can help avoid over wetting and over granulation of the product even when little moisture is used.

1.9.2.2 Agglomerating binders for the MADG process:

The binders used in the agglomeration stage should be easily wettable and become tacky with the addition of a small amount of water. Previous studies indicate that low-viscosity polyvinylpyrrolidones (PVPs) such as PVP K-12 are ideal for this purpose. If PVP is not an acceptable choice because of formulation concerns such as chemical compatibility, binders such as hydroxypropyl cellulose (HPC), crosspovidone, maltodextrins, sodium carboxymethylcellulose (Na CMC), or hydroxypropyl methylcellulose (HPMC) can be used instead. The binders can be used singly or in multiple combinations to achieve the desired effects or address specific concerns. If binders are available in various viscosity grades, it is desirable to use the ones with low viscosity because they tend not to retard tablet or capsule dissolution. However, binders with very low viscosity may not provide enough tackiness for agglomeration.

In general, high-viscosity binders are often required in small amounts. The amount of binder needed does not depend on the viscosity alone; other factors such as binder mass must be considered. For example, if 5% of PVP K-12 is sufficient for one formulation, 2% of PVP K-30 may not be the correct proportion for the same formulation. Experiments have shown that about 3% or more of PVP K-30 would be required for proper agglomeration. This difference results from the fact that, in addition to binder viscosity and tackiness, the mass of the binder also plays an important role in covering and coating the blend particles that are to be agglomerated. The binders with small particle size and great surface area would be advantageous as well. Generally,

binders such as HPC, Na CMC, and HPMC require more water and longer hydration time compared with PVP or maltodextrin. On the other hand, binders such as Starch 1500 would not be suitable for the MADG process because this binder has a significant percentage of unhydrolyzed starch components that could absorb considerable amounts of water. As a result, the amount of water needed to effect agglomeration when using Starch 1500 would not be practical for the development of a typical MADG formulation. Completely hydrolyzed starch is not recommended because it does not have sufficient tackiness to cause agglomeration. In all cases, the binder chosen should have fine particles and sufficient tackiness upon moistening to cause adequate agglomeration.

1.9.2.3 Moisture absorbents for the MADG process:

About 70–95% of any MADG formulation is agglomerated, and the remaining portion of excipients is added as is. In general, the non agglomerated portion consists of moisture absorbents, disintegrates, and lubricants. It is desirable that non agglomerated excipients be closer in particle-size distribution to the agglomerated portion of the formulation to minimize the potential for segregation. Microcrystalline cellulose, which doubles as a filler and moisture absorbent, is available in the approximate particle size of 200 μm. Low moisture grades are also available. Avicel PH 200 LM (FMC, Philadelphia) is an excipient with low moisture content (< 1.5% by weight, as determined by loss on drying). Aeroperl 300, a moisture absorbent in the form of a non-lumpy, free-flowing granulated silica consisting of ~30-μm spherical particles is also available from Evonik Industries (Essen, Germany). Granular Aeroperl 300 has excellent moisture-

absorbing capacity, and its surface area is much lower than that of the colloidal silica used as a glidant for granulation. The amount of Aeroperl 300 typically needed for the MADG formulation is small, which is advantageous from the standpoint of preventing tablet-ejection problems.

The disintegrant crospovidone is available in coarse particle-size grade from either ISP (Wayne, NJ) or BASF (Ludwigshafen, Germany). This material is not only a superdisintegrant, but is also compactable and acts as moisture absorbent. Overall, excipients such as Avicel PH 200 LM, Aeroperl 300, and the coarse grade of crospovidone for the non agglomerated portion of the MADG process can significantly improve the quality of the formulation and facilitate the process. If the recommended excipients are not available, regular microcrystalline cellulose (e.g., Avicel PH101, PH102, and PH200), regular silicone dioxide, and crospovidone can be used as substitutes.

1.9.2.4 Formulation assessment:

Assessment of the formulation itself is the next task to be completed once the wettability of the drug has been established. For most drugs, a preliminary formulation-development evaluation can be initiated with a small batch. For nonwettable drugs or high drug-loading formulations, additional agglomerating binder (e.g., PVP) and more water during the agglomeration stage might be required. In addition, for drugs that are more difficult to granulate, mannitol (e.g., Perlitol 160 C, Roquette, France) or ther wettable fillers can be used in place of lactose monohydrate to achieve the desired

granulation. Conversely, small amounts of binder and water are needed if the drug is easily wettable and self-granulating.

The ratio of Aeroperl 300 or other silicon-dioxide-type excipients to water should be kept to at least 1:1 by weight in the formulation. If PVP is not desirable in a given formulation, other agglomerating binders can be used, as described above.

1.9.2.5 Final formulation and optimization:

Using the knowledge gained from the formulation-screening experiments described above, a large batch can be manufactured with a high-shear granulator. The preliminary studies enable adjustments to be made to improve formulation characteristics such as granulation and tableting, which can be further optimized as needed. Upon the successful completion of optimization exercises, the accelerated stability of the formulation can be evaluated. The scale-up and design-space studies can be conducted as needed.

1.9.2.6 Mechanism of the MADG process:

The granule-formation mechanism in the MADG process is the same as that in conventional wet granulation. In both cases, it is a process of powder particle-size enlargement, often in the presence of water and binders, through wet massing and kneading. The main differences between these two granulation processes are the amount of granulating liquid used and the level of agglomeration achieved. In conventional wet granulation, substantially more water is used to create large and wet granules, and heat drying removes the excess water. This step is followed by milling to reduce the granule

size. In the MADG process, only a small amount of water is used to create agglomeration. Moisture distribution and absorption steps follow, and neither heat drying nor milling is needed.

1.9.2.7 Additional considerations for the MADG process:

Moisture in the MADG formulation:

The amount of water used in the MADG process is part of the formula composition. This amount is a fixed value in the formula and is determined during formulation development. For example, if 2.0% (w/w) water is used, the rest of the ingredients should make up the 98.0% (w/w) of the formula. Because the MADG process does not include a heat-drying step, the water added would not be intentionally removed from the formulation. Because moisture is added but not removed in the MADG process, what happens to the moisture and how it affects product quality might be causes for concern. To answer these questions, an MADG formulation that uses 1.5% water, 20% Avicel PH 200 LM, 1.5% Aeroperl 300, and other ingredients for a total weight of 100 g can be considered. First, 1.5 g of water is used in the agglomeration stage. During the moisture-absorbing and -distribution stage, 20.0 g of Avicel PH200 LM (with an inherent moisture level of 1.5%) can take 0.7 g of moisture, while 1.5 g of Aeroperl 300 can absorb 2.25 g of moisture from the wet agglomerates. As a result, the final granulation reaches its equilibrium moisture level, and neither Avicel PH200 LM nor Aeroperl 300 appears damp or lumpy. Such a MADG formulation would not have much more free water than that produced by a typical conventional granulation process. Even if only

regular Avicel PH200 (with a moisture content of ~5%) is used without Aeroperl 300 in the same formulation, the amount of the remaining moisture (0.8 g) would be well distributed in the other formulation excipients, thus resulting in a free-flowing final granulation Silicone dioxide in an MADG formulation sometimes may be preferred to minimize the risk of granulation caking during storage, to avoid flowability problems, and to reduce the chance of moisture-induced chemical instability. In general, unless the drug in the MADG formulation is moisture-sensitive, additional stability risks of the finished product would not be expected.

1.9.2.8 Required equipment for MADG:

MADG only requires two pieces of equipment: an appropriate granulator and an airless spray system.

1.9.2.9 Granulator:

The granulator can be a planetary or high-shear granulator, but the blades should be at the bottom (either top or bottom driven) and not exposed. This is necessary because the amount of water used is very small and added on top of the powder bed by a fine spray. If the blades were exposed, the water could hit the blades and cause loss of water, possibly creating wet lumps and nonuniform granulation. The granulator should not have dead spots or spots where material could stick. A chopper in the granulator is also useful.

1.9.3 Water delivery system/airless spray system:

The preferred mechanism to deliver water spray consistently would be an airless spray system, which enables the water to be directed onto the powder bed in a high-shear granulator. Any airless spray nozzle with a gear pump or pressure vessel, where the spray

pattern can be reproduced and the exact amount of water delivered, would be adequate. Spray nozzles with an orifice of 0.1 mm or 0.15 mm can be attached to a syringe to deliver a low (5–10 mL) volume of water for small experiments.

This process also requires an airless spray system that accurately delivers the desired amount of water in small (50–200 µm) droplets. The system should not have drips; peristaltic pumps, in particular, are not suitable. The gear pump or pressure vessel must also provide the right type of spray. At the developmental stage, however, an appropriate spray tip attached to a syringe is sufficient.

1.9.3.1 Granulation sizing and milling:

An optimized MADG formulation and process should not produce large lumps in the granulation that require sizing or milling. Therefore, once lubricant is blended in with the granulation, the result may be the final blend that can be directly used for tablet compression, encapsulation, or powder filling. At times, small amounts of lumps in the granulation may stem from material buildup on the blades, choppers, walls, or the bottom of the granulator during agglomeration. In such situations, it may be necessary to pass the granulation through a screen such as 10 meshes or any other suitable size. Often, sizing or sifting is needed only if the formulation or process contains imperfections.

SEDATIVE AND HYPNOTICS

Sedative and hypnotics: ***(KD Tripathi)***

A drug that subdues excitement and clams the subject without inducing sleep, though drowsiness may be produced. Sedation refers to decreased responsiveness to any level of stimulation is associated with some decrease in motor activity and ideation. **- Sedative.**

A drug that induces or maintain sleeps, similar to normal to arousable sleep, this is not to be the confused with "hypnosis" which means a trans like state in which the subject becomes passive and highly suggestible. **- Hypnotic.**

Classification of sedative drugs:

The classification of these drugs is below:

Barbiturates: These are divided into

Table 1.3: long acting, short acting and ultra short acting of barbiturate.

Long acting	Short acting	Ultra short acting
Phenobarbitone, Mephobarbitone.	Butobarbitone, Secobarbitone, Pentobarbitone.	Thiopentone, Methohexitone, Hexobarbitone.

a) **Benzodiazepines antagonist:**

May be divided according to primary use:

Table 1.4: Hypnotics, anti-anxiety and anti-convulsions of benzodiazepine antagonist

Hypnotic	**Anti-anxiety**	**Anti-convulsions**
Diazepam, Flurazepam, Nitrazepam, Flunitrazepam, Temazepam, Triazolam, Midazolam.	Diazepam, Chlordiazepoxide, Oxazepam, Alprazolam.	Diazepam, Clonazepam, ClobaSzem.

b) Newer non-benzodiazepine hypnotics:

This includes Zoplicne, Zolpidem.

LITERATURE SURVEY...

2. LITERATURE SURVEY

2.1 Literature survey:

Extensive literature review was made for understanding the study and there has been number of reports concerning the applications of MADG in the formulation of different types of dosage forms like immediate release /sustain release / controlled release matrix tablets. Literature review made by referring to various national and international journals, databases such as pharmaceutical technology Europe,inform healthcare and various other web resources along with general books for pharmaceutical scientists.

1. Aniruddha MR., *et al.*, (2001) have modified the moist granulation technique (MGT) to develop the controlled-release (CR) dosage forms of acetaminophen.The MGT, which involves agglomeration and moisture absorption, has only been applied to immediate-release dosage forms. Their results indicate that MGT appears to be applicable in developing a CR formulation. They added small amount of granulating fluid (water) to a powder blend to activate a dry binder (such as polyvinylpyrrolidone [PVP] at 2% and 3.6%) and to facilitate agglomeration. Then, they added a moisture-absorbing material (microcrystalline cellulose [MCC]) to absorb any excess moisture. There by avoided the drying step. They have prepared acetaminophen CR tablets using hydroxypropylcellulose as the controlled-release agent and lactose fastflo® and dicalcium phosphate as the diluents. And they have also compared the MGT with conventional WG and direct compression (DC) processing methods. Finally in conclusion MGT can be applicable in developing a CR formulation.

2. Christensen LH., *et al.*, (2009) have examined the applicability of a 25 liter high shear mixer for MADG. MCC, potato starch or a mixture of 50% w/w of each was used as moisture absorbing material. The effects of water content, wet massing time, moisture absorbing material and dry mixing time on the size distribution, and the compressibility of the granulations were investigated. Tablets were compressed on a single punch press from all the granulations and on a rotary press from a few of the granulations. The results of the physical properties of the tablets revealed that the tablets primarily affected by the water content, the moisture absorbing material, and the compression force. Tablets with low mass variation, high crushing strength, low friability, and short disintegration time were achieved with both tablet presses by using a mixture of MCC and potato starch as moisture absorbing material.

3. Railker AM., *et al.*, (2000) have performed the evaluation &comparison of a MGT to conventional methods. They have prepared acetaminophen tablets using PVP as binder and MCC as moisture-absorbing material. Water was used as the granulating fluid. They compared of the MGT with DC and WG methods were accomplished by sieve analysis (particle size) and density measurements. They found that MG provided an increase in particle size compared to DC; these results were compared to those from the traditional WG after drying and screening. Finally can conclude that the MGT appears to have potential for the development of CR formulations.

4. Hausman DS., (2004) has compared the processes of low shear, high shear, and fluid bed granulation during low dose (0.1%) immediate release tablet development using three processing methods. They used similar formulations to evaluate low shear, high shear, and fluid bed granulation methods. For each granulation process, they dissolved or

suspended in the granulating fluid (water/methanol) and sprayed into the granulator. For low shear, high shear and fluid bed granulation, Patterson-Kelley V-Blender, GRAL and Diosna are used as equipment, respectively. Acceptable content uniformity was obtained using each technology. In conclusion, they found that the type of granulator and granulating solvent affected the granulation particle size distributions and bulk/tap densities. However, the addition of extra granular MCC minimized the effect of variable granulation properties and allowed similar tablets to be produced from each granulation process.

5. Railkar AM., *et al.*, (2001) have studied the effects of formulation factors on the MGT for CR tablets.CR tablets were prepared by the MGT, with acetaminophen and the polymer hydroxypropylcellulose as the controlled-release agent. The effects of varying drug, binder (PVP), polymer, and MCC levels on granule properties and tablet dissolution were studied. They performed dissolution testing in distilled water using the USP paddle method. In all cases, the granules flowed and compressed well. The granule properties were evaluated by calculating the mean particle size for all batches from sieve analysis data. In conclusion, the results showed that MGT can be applied to control drug release, and at a polymer content of 44.6% or more.

6. Chih-Ming C., *et al.*, (1900) have performed the comparison of MADG process with two conventional granulation methods i.e. WG and DG with a roller compactor, as well as with a DC formulation method for cohesive and fluffy sematilide hydrochloride tablets. They found that the granules produced by MADG with excellent flow ability which were equivalent in a number of ways to those produced by either conventional WG or DG and which were much better than the powder blend from the DC formulation. It is

proved that the tablets prepared using the MADG method has better content uniformity than those made using material from wet and dry granulation processes. Other tablet properties, such as weight variation, friability and dissolution, were similar among the tablets produced by the four processes.

7. Carstensen JT., (2002) has examined the effect of moisture on the stability of solid dosage forms prepared with aspirin as a model drug candidate. Usually aspirin is not prepared by WG. Even though he driven off water in a WG, there is still sufficient moisture stress in the process to induce excessive decomposition on subsequent storage. In other instances, the results of the moisture sensitivity of a drug may be used to apply a hard shall capsule approach. This presumes that the drug substance is not particularly hygroscopic, since otherwise, the capsule shell will provide an unwanted source of moisture.

8. Bayomi MA., *et al.*, (2001) have prepared the sustained-release (SR) theophylline (TPH) tablets by applying the MADG. The interaction between the excipients sodium alginate (SAL) and calcium gluconate (CG) was the base for the formation of a cross-linked matrix that may regulate TPH release from the formulated tablets. The prepared granules showed good physical characteristics concerning the flow properties and compressibility, with the angles of repose in the range 29-31, and the compressibility indices ranged between 15% and 25%. The granules had low friability values (3.0%-4.2%), depending on SAL: CG ratios. The resulting tablets showed good physical properties, with a lower rate of drug release compared with the commercial TPH tablets (Quibron®). They found that the release of TPH from the tablets was not markedly affected by either the concentration of added dry binder (carbopol 934) or the tablet

hardness, indicating that the rate-determining step in drug release was the diffusion. Tablets formulated with equal ratios of CG and SAL that showed good physical properties and slow TPH release were chosen for bioavailability studies in beagle dogs, and results were compared with those for Quibron. The *in-vivo* data showed a comparable plasma concentration profile for both tablet formulations, with prolonged appearance of drug in the plasma up to 24 hrs.

9. Rajnibala., *et al*., (2009) have worked to prepare bitterless mouth dissolving tablets of Zolpidem Tartrate using ion exchange resin Tulsion 335 as a taste masking agent. Method: Ion exchange resinates and tasteless granules were prepared with Tulsion 335 in weight ratio of 1:3. Resinates and granules were evaluated for its taste sensation in human volunteers. Prepared complex was further examined through IR, DSC and XRD curves. The mouth dissolving tablets of both resinates and granules were prepared with two superdisintegrants e.g. crosscarmellose sodium and crospovidone in different concentration. The blend was examined for their flow properties. The tablets were evaluated for physiochemical properties. The tasteless blends having good flow properties. The prepared zero defect mouth dissolving tablets were passed all the official and non-official parameters. The disintegration time was also tested and was found to be less than one minute. A tablet having resinates shows less time for onset of action of drug due to enhanced and fast release of Zolpidem Tartrate.

10. Rahul K.Amrutkar., *et al*., (2011) in the present study attempt has been done to formulate and evaluate the fast dissolving sublingual tablet of Zolpidem Tartrate. Tablets were prepared by wet granulation method using superdisintegrants, Sodium starch glycolate and Cross-povidone. Camphor was added in the formulation as a sublimating

agent. The tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, and disintegration time and dissolution study. Among studied formations hardness was found in 3-3.5 kg/cm2 range and friability less than 1%.Weight variation taste complies with pharmacopoeias limits. Sublimation of Camphor from tablets resulted in better tablets as compared to the tablets prepared from granules that were exposing to vacuum. The systematic formulation approach helped in understanding the effect of formulation processing variables.

11. XIE Qi-ang., e*t al*., (2009) have worked to prepare a double pulse control release pellets of Zolpidem Tartrate and investigate the dissolution influence factor in vitro. METHOD: The kind and amount of disintegrant were screened using uniform design and single factor design. Core contented drug was prepared by Extrusion-spheronization. The surface was improved using coating lactose with Pharmacoat 606. The single pulse release pellets were prepared by coating a control release layer with Ethyl cellulose aqueous dispersion （Surelease E-7-19040）. The double pulse pellets were prepared by loading drug and coating film with Pharmacoat 606. The times of beginning and completing of dissolution were defined when cumulative percentages of drug dissolution were 5.00% （t 0.05）and 90.00%（t0.9）. The time was as lag-time if the cumulative percentage of drug dissolution was less than 5.00%. Crosscamellose sodium was a suitable disintegrant. t 0.9 of the first and second pulse dosage were about 30 and 45 min respectively. t lag-time was about 150 min. The factors such as disintegrant amount, pellet diameter, weight percentage of control release layer, the progress of finishing, drug contented layer loading, film coating will affect the in vitro dissolution. The pH value of

dissolution medium shows no influence on the dissolution in vitro.The pellets has an ideal double pulse release.

12. Estelle Weinling., *et al*., (2006) have worked to Compared the relative bioavailability and the pharmacokinetic profile of a single oral dose of a Zolpidem modified-release (MR) 12.5-mg formulation with those of the standard 10-mg Zolpidem immediate-release (IR) formulation. Absolute bioavailabilities of oral formulations were evaluated using intravenously (i.v.) administered Zolpidem as a reference. The initial absorption phase of the Zolpidem-MR formulation was as fast as that of Zolpidem-IR with no significant difference in t_{max}. With Zolpidem-MR 12.5 mg, C_{max} was moderately lower than with Zolpidem-IR (ratio of 0.82), and plasma Zolpidem concentrations were maintained above those observed with Zolpidem-IR for a longer period of time, particularly from 3 to 6 h post-dose. This was confirmed by an increase in half-value duration (HVD) from 2.3 h with Zolpidem-IR to 4.6 h with Zolpidem-MR 12.5 mg. The mean terminal half-life was similar between formulations. Zolpidem-MR 12.5 mg provides the appropriate pharmacokinetic characteristics to extend plasma Zolpidem concentrations into the middle of the night (3–6 h post-dose), while retaining the same t_{max} and terminal half-life.

13. Hardik M Prajapati., *et al*., (2012) studied to design controlled porosity osmotic pump (CPOP) tablets of Zolpidem Tartrate. The porous osmotic pump contains pore forming agent (PEG-400) in the coating membrane which after coming in contact with water, dissolve, resulting in an in situ formation of microporous structure. The effect of different formulation variables, namely, ratio of drug to osmogent, membrane weight gain and level of pore former on the in-vitro release was studied using by different ratio

of drug to osmogent and different concentration of pore forming agent. Cellulose acetate (4%) was used as the semi permeable membrane. Drug excipients compatibility was studied by FTIR and it indicated that there was no interaction between drug and excipients. Microporous structure of coating membrane of optimized formulation F4C3 was determined by Scanning Electron Microscope (SEM). Drug release was inversely proportional to membrane weight gain however, directly related to the level of pore former in the membrane. Optimized formulation (F4C3) was found to deliver 50% of total dose within 30 minute and above 90% of drug (Zolpidem Tartrate) at the end of 4 hours.

14. Shailesh T. Prajapati*., et al*., (2011) Present investigation describes the influence of the concentration of PEG 6000 as a melt binder and ratio of HPMC K4M: PVP on Zolpidem Tartrate controlled-release tablet formulations using 3(2) full factorial design. Tablets were prepared by melt granulation technique and evaluated for various evaluation parameters. It was observed that concentration of melt binder had significant effect on Q(1), Q(4), n, and K Binder concentration 25% w/w was found optimum. Optimized formulation (F7)) showed good similarity with theoretical profile of drug. The X(2) variable had a significant effect on dependent variables, and the X(1) variable had no significant effect on dependent variables.

15. Cynthia Kirkwood., *et al*., (2007) Zolpidem modified-release (MR) is the first hypnotic agent to be marketed in an extended-release formulation. Zolpidem MR is a two-layered, biphasic release tablet indicated for the management of induction of sleep and sleep maintenance. The pharmacokinetics of the drugs are similar to those of immediate-release Zolpidem. Two double-blind, placebo-controlled, parallel-group trials

demonstrated efficacy in adults and elderly patients treated with Zolpidem MR for 3 weeks without significant impairment in next-day psychomotor functioning. The most common adverse effects with Zolpidem MR were dizziness, somnolence, and headache. A starting dose of Zolpidem MR 12.5 mg is recommended for adults and 6.25 mg for elderly patients.

16. Moen MD., ***et al*****., (2006)** Zolpidem extended-release(ER) or controlled-release (CR), is a new formulation of Zolpidem, a nonbenzodiazepine hypnotic. It is indicated in the US for the treatment of insomnia, characterised by difficulties with sleep onset and/or sleep maintenance. Zolpidem CR is a dual-layered tablet; one layer releases Zolpidem immediately and a second layer provide a slower release of additional Zolpidem for maintenance of plasma Zolpidem concentrations. Efficacy of Zolpidem CR was assessed in two 3-week, randomized, double-blind, placebo-controlled, phase III polysomnography trials in younger adult (aged 18-64 years) or elderly (aged > or =65 years) patients with primary insomnia. Patients received nightly Zolpidem CR (12.5mg in younger adult and 6.25mg in elderly patients). Efficacy was assessed objectively on nights 1, 2, 15 and 16. Patients who received Zolpidem CR had significantly improved objective latency to persistent sleep, wake time after sleep onset and sleep efficiency on assessment nights compared with placebo recipients. In subjective assessments of sleep quality on day 2 and nights 15 and 22, significantly more Zolpidem CR than placebo recipients gave favourable responses on a Patient Global Impression scale in the study in younger adult patients. In the other study, significantly more elderly patients in the Zolpidem CR group rated their sleep as improved compared with the placebo group.

Zolpidem CR was generally well tolerated and appears to have a tolerability profile similar to that of the original formulation of Zolpidem.

DRUG PROFILE

(Wikipedia, www.drugbank.com, 2001, United state Pharmacopoeia, 2007)

2.2 Drug profile:

ZOLPIDEM TARTRATE

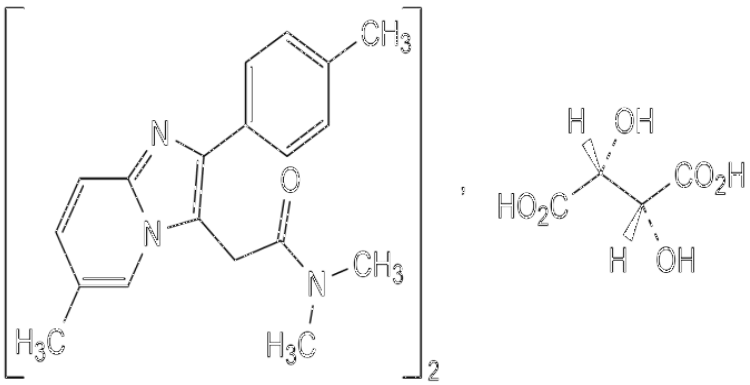
Generic Name:

Zolpidem Tartrate.

Brand names:

Ambien CR, Lorex, Stilnoct.

Structure:



Category:

Sedative and hypnotic.

Chemical Name:

N, N-dimethyl-2-[6-methyl-2-(4-methylphenyl) imidazo [1, 2-a] pyridin-3-yl] acetamide

Molecularweigh:

307.3895.

Molecular formula:

$C_{19}H_{21}N_3O$.

Physical appearance:

White to off-white powder.

Solubility:

Soluble in water, sparingly soluble in methanol and practically insoluble in methylene chloride.

State:

Solid.

Melting point:

218^0C

Clinical Pharmacology:

Indication:

For the short-term treatment of insomnia.

Mechanism of Action:

Zolpidem modulates the alpha-subunit, known as the benzodiazepine receptor, within the $GABA_A$ receptor chloride channel macromolecular complex. Unlike the benzodiazepines, which non-selectively interact with all three alpha-receptor subtypes, Zolpidem preferentially binds to the alpha-1 receptor.

Pharmacokinetics and Metabolism:

Absorption:

Zolpidem is rapidly absorbed from the GI tract.

Protein binding:

92.5 ± 0.1% (independent of concentration between 40 and 790 ng/mL).

Metabolites:

Zolpidem is converted to inactive metabolites in the liver.

Route of elimination:

Zolpidem Tartrate tablets are converted to inactive metabolites that are eliminated primarily by renal excretion.

Half life:

2.6 hours.

Toxicity:

Oral (male rat) LD_{50} = 695 mg/kg. Symptoms of overdose include impairment of consciousness ranging from somnolence to light coma.

Pharmacodynamics:

Zolpidem is a sedative or hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties. It interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-selectively bind to and activate all three alpha receptor subtypes, Zolpidem in vitro binds the (alpha1) receptor preferentially. The (alpha1) receptor is found primarily on the Lamina IV of the sensor motor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus.

Adverse effects:

Nausea, vomiting, dizziness, anterograde ammensia. Hallucinations, through all physical senses, of varying intensity. Delusions, altered thought pattern, axia or poor

motor coordination, difficulty maintaining balance. Euphoria or dysphoria, increase apatite, increase or decrease libido, amnesia, short term memory loss.

Drug-drug interactions:

Notable drug-drug interactions with pharmacokinetics of Zolpidem includes chlorpromazine, fluconazole, imipramine, itraconazole, keloconazole, ritampicine and ritonavir interactions with carbamazipine and phenytoin can be expected based on this metabolic pathways, but have not yet been studied. Theredoes not appeared to be any interaction between Zolpidem and cimetidine or ranitidine.

EXCIPIENT'S PROFILE

2.3 Excipients profile: *(Raymond C Rowse, Paul J Weller, 2003)*

LACTOSE MONOHYDRATE

Nonproprietary Names:

BP : Lactose monohydrate.

PhEur : Lactosum monohydricum.

JP : Lactose.

USPNF : Lactose monohydrate.

Synonyms:

Lactochem Coarse Crystals, Lactochem Crystals, Lactochem Fine Crystals, Lactochem Extra Fine Crystals, Pharmatose DCL 15, Pharmatose 50M, Pharmatose 80M, NF Lactose 310, NF Lactose 312, NF Lactose 313, CapsuLac 60, GranuLac 70, GranuLac 140, GranuLac 200 ,GranuLac 230 ,PrismaLac 40

Chemical Name:

O-b-D-Galactopyranosyl-(14)-a-D-glucopyranose monohydrate

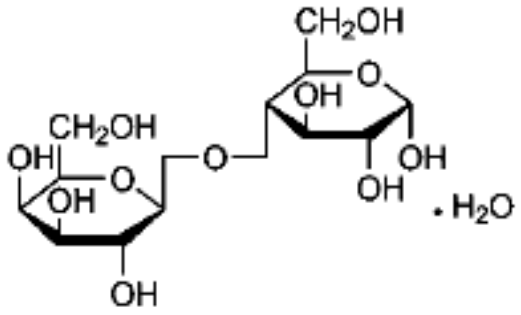
Empirical Formula:

$C_{12}H_{22}O_{11}$ H_2O.

Molecular Weight:

360.31.

Structural formula:



α-Lactose monohydrate

The USPNF 23 describes lactose monohydrate as a natural disaccharide, obtained from milk, which consists of one galactose and one glucose moiety. The PhEur 2005 describes lactose monohydrate as the monohydrate of O-β -D-galactopyranosyl-(1→4)-α -D-glucopyranose. It is stated in the USPNF 23 that lactose monohydrate may be modified as to its physical characteristics, and may contain varying proportions of amorphous lactose.

Description:

In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. α-lactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous. The stable crystalline forms of lactose are a-lactose monohydrate, b-lactose anhydrous and stable a-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while α-lactose is 40% as sweet.

Functional category:

Binding agent, diluents for dry-powder inhalers, tablet binder, tablet and capsule diluent.

Applications in pharmaceutical formulation or technology:

Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas.(1–13) Lactose is also used as a diluent in dry-powder inhalation.(14–16) Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently. Other applications of lactose include use in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose (approximately 1: 3) to prepare sugar-coating solutions. Direct-compression grades of lactose monohydrate are available as granulated/agglomerated a-lactose monohydrate, containing small amounts of anhydrous lactose. Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation. Other directly compressible lactose's are spray-dried lactose and anhydrous lactose. See Lactose, Spray-Dried, Lactose, Anhydrous.

Stability and storage conditions:

Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. The purities of different lactose's can vary and color evaluation may be important, particularly if white tablets are being formulated. The colour stabilities of various lactose's also differ. Lactose should be stored in a well-closed container in a cool, dry place.

MICROCRYSTALLINE CELLULOSE

Nonproprietary Names:

BP : Microcrystalline cellulose.

JP : Microcrystalline cellulose.

PhEur : Cellulosum microcristallinum.

USPNF: Microcrystalline cellulose.

Synonyms:

Avicel, celex, tabulose, pharmacel, fibrocel, emocel, crystalline celluose.

Cellulose gel, ethispheres, tabulose, vivapur.

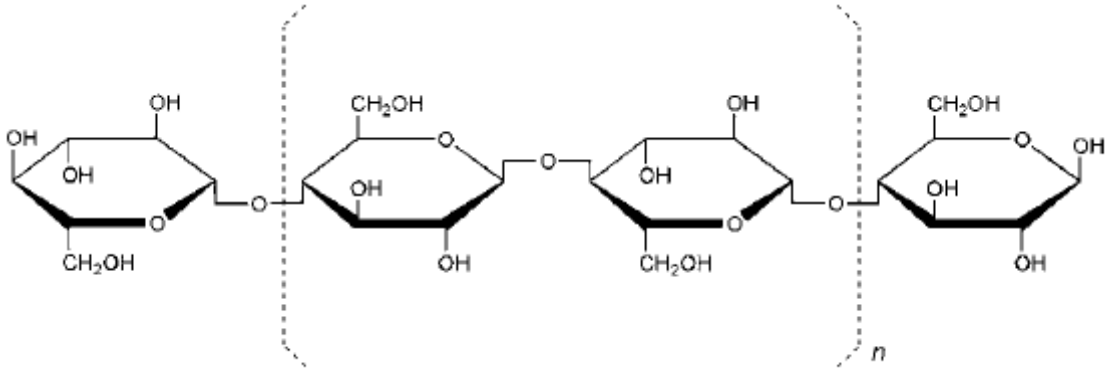
Chemical Name:

Cellulose.

Empirical formula:

$(C_6 H_{10} O_5)$ n; where n-220.

Structural formula:



Description:

It is purified, partially depolymerized cellulose that occurs as white, odorless, tasteless, crystalline powder composed of porous particles.

Molecular weight:

36000.

Functional Category:

Tablet/capsule binder, adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.

Melting point:

Chars at 260-270°C.

Solubility:

Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids, and most organic solvents.

Applications:

1. It is widely used as a disintegrant in tablets and capsules.

2. It is used in both wet granulation and direct compression processes and as tablet disintegrant.

3. It has both binding and disintegrating action.

Uses of Microcrystalline cellulose:

Table 2.1: uses of microcrystalline cellulose

Use	Concentration
Absorbent	20-90
Anti-adherent	5-20
Capsule binder/diluents	20-90
Tablet disintegrant	5-15
Tablet binder/diluents	20-90

Stability and storage:

It is stable though hygroscopic material. The bulk material should be stored in well closed container in a cool and dry place.

Incompatibilities:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

SODIUM STARCH GLYCOLATE

Nonproprietary names:

BP : sodium starch glycolate

PhEur : carboxymethylamylum natricum

USPNF: sodium starch glycolate

Synonyms:

Carboxymethyl starch, sodium salt, explosol, explotab, glycolys, primojel, starch carboxymethyl ether, sodium salt, tablo, vivastar P.

Chemical name:

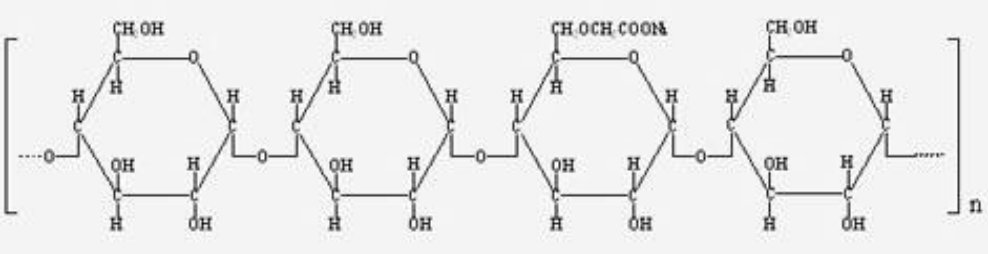
Sodium carboxymethyl starch.

Empirical formula and molecular weight:

The USPNF 23 states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch, containing 2.8-4.2% sodium. The phEur2005 describes three types of material. Types A and B occurs as the sodium salt of a cross-linked partly O-carboxymethylated starch, containing 2.8-4.2% and 2.0-3.4% of sodium respectively. Type C is the sodium salt of a cross-linked by physical dehydration, partly O-carboxymethylated starch, containing 2.8-5.0% sodium. The JP, PhEur and USPNF monographs have been harmonised for type A and type B variants.

Sodium starch glycolate may be characterized by the degree of substitution and crosslinking. The molecular weight is typically 5x105-1x106.

Structural formula:



Functional category:

Tablet and capsule disintegrate.

Description:

Sodium starch glycolate is a white to off-white, odorless, tastless, free-flowing powder. The phEur 2005 states that it consists of oval or spherical granules, 30-100 **µm** in diameter, with some less-spherical granules ranging from 10-35**µm** in diameter.

Typical properties:

Acidity/alkalinity:pH=3.0-5.0 or pH=5.5-7.5 for a 3.3%w/v aqueous dispersion.

Density: 0.756 g/cm3

Solubility:

Sparingly soluble in ethanol (95%), practically insoluble in water. At a concentration of 2%w/v sodium starch glycolate disperses in cold water and settles in the form of a highly hydrated layer. Viscosity (dynamic):200mpa s (200 cp) for a 4%w/v aqueous dispersion. Viscosity is 4.26 mp as for a 2%w/v aqueous dispersion.

Stability and storage conditions:

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

The physical properties of sodium starch glycolate remain unchanged for up to 3-5 years if it is stored at moderate temperatures and humidity

Applications in pharmaceutical formulation or technology:

Sodium starch glycolate is widely used in oral pharmaceutics as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct compression or wet-granulation processes. The usual concentration employed in a formulation is between 2%and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Although the effectiveness of many disintegrates is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time. Sodium starch glycolate has also been investigated for use as a suspending vehicle.

MAGNESIUM STEARATE

Nonproprietary Names:

BP : Magnesium Stearate

JP : Magnesium Stearate

PhEur : Magnesium Stearate

USPNF: Magnesium Stearate

Synonyms

Dibasic magnesium stearate, magnesium distearate, magnesia stearas, magnesium octadecanoate, octadecanoic acid, magnesium salt, Stearic acid, magnesium salt, synpro 90.

Chemical Name:

Octadecanoic acid magnesium salt.

Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$, 591.24.

The USP32-NF27 describes magnesium stearate as a compound of magnesium with a mixture of organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 6.5 describes magnesium stearate as a mixture of solid organic acids consisting mainly of variable proportions of magnesium stearate and magnesium palmitate obtained from sources of vegetable or animal origin.

Structural Formula:

$[CH_3(CH_2)16COO]_2Mg$.

Functional Category:

Tablet and Capsule lubricant.

Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations, it is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Description:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of Stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Crystalline forms:

High-purity magnesium stearate has been isolated as a trihydrate, a dehydrate, and anhydrate.

Density (bulk):

0.159 $g/cm^{3.}$

Density (tapped):

0.286 $g/cm^{3.}$

Density (true):

1.092 $g/cm^{3.}$

Flash point:

250^{O} C.

Flowability:

Poorly flowing, cohesive powder.

Melting range:

117-150^{O} C (commercial samples);

126-130^{O} C (high purity magnesium stearate).

Solubility:

Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Specific surface area:

1.6 - 14.8 m^2/g.

Stability and Storage conditions:

Magnesium stearate is stable and stored in a well-closed container in a cool, dry place.

Related Substances:

Calcium stearate, magnesium aluminum silicate; Stearic acid; zinc stearate.

WATER

Nonproprietary Names:

BP : Purified water

JP : Purified water

PhEur : Aqua purificata

USPNF: Purified water

Synonyms:

Aqua, hydrogen oxide.

Chemical Name:

Water.

Empirical Formula and Molecular Weight:

H_2O & 18.02.

Structural Formula:

H_2O.

Descriptions:

The term ‘water’ is used to describe potable water that is freshly drawn direct from the public supply and is suitable for drinking. The chemical composition of potable water is variable and the nature and concentrations of the impurities in it depend upon the source from which it is drawn. Although potable water must be both palatable and safe to drink, for most pharmaceutical applications potable water is purified by distillation, ion exchange treatment, reverse osmosis, or some other suitable process to produce ‘purified water’. For certain applications, water with pharmacopeias specifications differing from

those of purified water should be used, e.g. water for injection. Water is a clear, colorless, odorless, and tasteless liquid.

Typical applications of specific grades of water:

Table 2.2: typical applications of water of specific grades of water

Type	Use
Bacteriostatic water for Injection.	Diluent for ophthalmic and multiple-dose Injections
Potable water	Public supply suitable for drinking, the purity of which is unlikely to be suitable for use in The manufacture of pharmaceuticals.
Purified water	Vehicle and solvent for the manufacture of drug products and pharmaceutical preparations; not suitable for use in the Manufacture of parenteral products.
Sterile water for Inhalation	Diluent for inhalation therapy products.
Sterile water for Irrigation	Diluent for internal irrigation therapy products.
Water for injections in Bulk	Water for the bulk preparation of medicines for parenteral administration.

Stability and storage conditions:

Water is chemically stable in all physical states (ice, liquid, and vapor). Water for specific purposes should be stored in appropriate containers.

Incompatibilities:

In pharmaceutical formulations, water can react with drugs and other excipients that are susceptible to hydrolysis (decomposition in the presence of water or moisture) at ambient and elevated temperatures. Water can react violently with alkali metals and rapidly with alkaline metals and their oxides, such as calcium oxide and magnesium oxide. Water also reacts with anhydrous salts to form hydrates of various compositions, and with certain organic materials and calcium carbide.

AIM & OBJECTIVES....

3. AIM AND OBJECTIVES

Aim:

The aim of the present study is to develop the Zolpidem Tartrate tablets by Process development and Optimization of Moisture activated dry granulation technique.

Objective:

- Objective of this present study is to develop the Zolpidem Tartrate tablets using Moisture activated dry granulation technique.
- To optimize the water uptakes in the developmental stages of the formulation based on MADG.
- To carry out the evaluation tests for the finished product
- To establish *In–vitro* drug release compliance with the established criteria.

PLAN OF WORK....

4. PLAN OF WORK

- **Literature survey**.
- **Materials and equipments.**
- **Pre-formulation studies.**
  - **Characterization of Drug.**
    - Colour and Appearance.
    - Melting Point Determination.
    - Solubility Study.
  - **Identification of drug.**
    - FTIR Spectroscopy.
    - UV – spectral analysis.
    - Loss on drying.
  - **Drug – Excipients compatibility studies.**
    - Differential scanning calorimetry (DSC) Analysis.
  - **Preparation of granules and Evaluation of granules.**
    - Angle of repose.
    - Loose bulk density.
    - Tapped bulk density.
    - Carr's index.
    - Haursner's rat

- **Formulation of tablets.**
- **Evaluation of tablets.**
  - **Physico-chemical properties of tablets.**
    - Colour and Appearance.
    - Thickness and size.
    - Weight variation.
    - Drug content.
    - ***In-vitro* drug release studies.**
    - **Stability studies.**
- **Results and Discussion.**
- **Summary and Conclusion.**
- **Future Prospects.**
- **Bibliography.**

MATERIALS & EQUIPMENTS....

5. MATERIALS AND EQUIPMENTS

5.1 List of Materials used with sources:

Table 5.1: List of Materials and their Suppliers

S. no	Name of Material	Supplied by
1	Zolpidem Tartrate	Aurabindo pharma ltd, jadcherla
2	Lactose monohydrate	Aurabindo pharma ltd, jadcherla
3	Microcrystalline cellulose	Aurabindo pharma ltd, jadcherla
4	Sodium starch glycolate	Aurabindo pharma ltd, jadcherla
5	Water	Aurabindo pharma ltd, jadcherla
6	Magnesium stearate	Aurabindo pharma ltd, jadcherla

5.2 List of Equipments used with model:

Table 5.2: List of equipments with their make and model

S. no	Name of the equipment	Make	Model
1	Electronic balance	Shimadzu, Japan	BL-200H.
2	UV-Visible spectrophotometer	Shimadzu, Japan	1800
3	FTIR Spectrophotometer	Bruker	----
4	Dissolution test apparatus	Pharma test	
5	Disintegration apparatus	Electrolab USP	ED-2AL
6	Vibro shifter	Bectochem	L1610
7	Tap density apparatus	Indo labs, Chennai	VTAP-M-2
8	Melting point test apparatus	Precision scientific co., Chennai	---
9	Rapid mixing granulator	Sainath pvt ltd	---
10	Hardness tester	Dr.schleuiniger Pharmatron	---
11	Roche friabilitor	Electrolab	EF-2
12	IR moisture analyzer	Sorties	---
13	Compression mission	Pacific tools ltd	---
14	Vernier caliper	Mitutoyo	---

PRE-FORMULATION STUDIES....

6. PRE-FORMULATION STUDIES

6.1 Characterization of drug:

6.1.1 Colour and appearance: *(United State Pharmacopoeia, 2007)*

The sample was observed visually.

6.1.2 Melting point:

Melting point of drug was determined by Melting point test apparatus.

6.1.3 Solubility: *(United state Pharmacopoeia, 2007)*

Solubility study was carried out as per the I.P.2007.In this maximum amount of solvent required to dissolve the solute was determined.

6.1.4 Identification of drug:

6.1.4.1 Identification of drug by FTIR spectroscopy: *(Robert M. Silverstein, 2003)*

FTIR study was carried out to identify drug. Infrared spectrum of Zolpidem Tartrate was determined on Fourier transform Infrared Spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run followed by using Bruker- FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

6.1.4.2 Spectroscopic studies of Zolpidem Tartrate:

6.1.4.2.1 UV Spectral analysis of Zolpidem Tartrate:

6.1.4.2.2 UV spectral analysis of Zolpidem Tartrate in distilled water:

6.1.4.2.2.1 Determination of λmax of Zolpidem Tartrate in distilled water:

Weighed accurately about 25mg of Zolpidem Tartrate in a 25 ml volumetric flask added 10 ml of distilled water sonicate to get clear solution and made up the volume with distilled water. From the above solution pipette out 0.1ml by using micro pipette in to 10ml volumetric flask, made up the volume with distilled water to get the concentration of 10 µg/ml solution. The solution was scanned in the range of wavelength 200 – 400 nm. The λ_{max} was recorded using double beam UV-Visible spectrophotometer.

6.1.4.2.2.2 Preparation of calibration curve of Zolpidem Tartrate:

Preparation stock solution:

Weighed accurately about 25 mg of Zolpidem Tartrate raw material (API) in 25ml Volumetric flask add 10ml of distilled water and sonicate to get clear solution and make up the volume with distilled water to get mg/ml solution. From the stock solution pipette out 1ml into a 10 ml volumetric flask and made up to the volume with distilled water to get 100µg/ml solution, prepared concentration ranges of 2-20µg/ml were prepared and scanned at 266nm.

6.1.4.2.2.3 Assay of Zolpidem Tartrate:

Procedure:

Weighed accurately about 25 mg of Zolpidem Tartrate raw material (API) in 25ml volumetric flask add10 ml of distilled water and sonicate to get clear solution and make up the volume with distilled water to get 1mg/ml solution. From the stock solution pipette

out 0.1ml into a 10 ml volumetric flask and made up to the volume with distilled water to get 10µg/ml solution.

6.1.5 Loss on drying: *(United state Pharmacopoeia, 2007)*

Loss on drying is the loss of weight expressed as percentage w/w resulting from volatile matter of any kind that can be driven off under specified condition. The test can be carried out on the well mixed sample of the substance.

$$\text{Loss on drying} = \frac{\text{Initial weight of substance} - \text{Final weight of substance}}{\text{Initial weight of substance}} \times 100$$

6.2 Drug - excipients compatibility studies:

Drug excipients studies holds great importance in designing a formulation In drug formulation it is essential to evaluate the possible interactions between the active principle and the excipients, as the choice of the excipients should be performed in relation to the drug delivery, to their compatibility with the same drug and to the stability of the final product.

6.2.1 Differential scanning calorimetry study (DSC): *(Jain N. K., 2008))*

Zolpidem Tartrate powder was mixed with various excipients in the ratio of 1:1.The mixture of drug with excipients to maximize the like hood of obscuring an interaction. Mixture should be examined under Nitrogen to eliminate oxidative and pyrolytic effect at a standard heating rate (2, 5 or 10^0C/minute) on DSC. Over a temperature range, which will encompass any thermal changes due to the mixture of drug with polymers? Thermo grams of pure drug are used as a reference.

Appearance or disappearance of one or more peaks in thermo grams of drug with excipients are considered as an indication of interaction.

6.3 Preparation and evaluation of granules:

6.3.1 Preparation of granules:

All ingredients were weighed and passed through mesh #40 separately and Zolpidem Tartrate passed through mesh #30. The drug and excipients were blended first in mortar and pestle then the remaining ingredients are added in that and blended for 20 min. Finally the blend is passed through mesh #20 and used for evaluation of flow characteristics.

6.3.2 Evaluation of micromeritic properties of granules:

6.3.2.1 Angle of repose: *(Aulton M.E, 2002,)*

The angle of repose, was determined by the funnel method. The accurately weighed (10 gm) granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of granules. The granules were allowed to flow through the funnel freely onto a clean surface. The diameter of the granules cone was measured and angle of repose was calculated using the following equation:

$$\tan \theta = h/r$$

Where ‘h’ is the height of granules cone and ‘r’ is the radius of the granules cone. Relationship between angle of repose (θ) and flowability is shown in the Table 6.1.

Table 6.1: Relationship between Angle of repose (θ) and Flowability

S. no	Angle of repose(θ)	Flowability
1	<20	Excellent
2	20 – 30	Good
3	30 – 35	Passable
4	>40	Very poor

6.3.2.2 Loose bulk density and Tapped bulk density:

An accurately weighed (30 gm) granules from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the granules was measured which give bulk volume. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. Both Loose Bulk Density (LBD) and Tapped Bulk Density (TBD) of granules were determined using the following formulae.

LBD = Weight of the granules/Volume of the granules

TBD = Weight of the granules/Tapped volume of the granules.

6.3.2.3 Carr's Compressibility index:

The compressibility index of the granules was determined using following Carr's compressibility index formula.

Carr's Compressibility Index (%) = [(TBD-LBD)/ TBD] x100

Relationship between % compressibility and flowability is shown in the Table 6.2.

Table 6.2: Relationship between % Compressibility index and Flowability

S. no	% Compressibility index	Flowability
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-35	Poor
5	33-38	Very poor
6	>40	Very very poor

6.3.2.4 Hausner's ratio:

Hausner's ratio is the ratio between tapped density and bulk density. Hausner's ratio less than 1.25 indicates good flow properties while Hausner's ratio greater than 1.25 shows poor flow of granules.

Hausner's ratio = Tapped bulk density / loose bulk density

Table 6.3: Relationship between Hausner's ratio and Flowability

S. no	Hausner's ratio	Flow Property
1	0.0 - 1.25	Free flow
2	1.25 - 1.6	Cohesive flow

FORMULATION OF TABLETs…

7. FORMULATION OF TABLETS

7.1 Experimental design:

7.1.1 Unit formula and quantitative details of Zolpidem Tartrate 5mg:

Table 7.1: unit formula and quantities details of Zolpidem Tartrate 5mg

S. no	Ingredients	Unit formula(mg)	%content
1	Zolpidem Tartrate	5.00	8.33
2	Lactose monohydrate	43.80	73
3	Microcrystalline cellulose	10	16.6
4	Sodium starch glycolate	0.60	1
5	Purified water	q.s	-
6	Magnesium Stearate	0.60	1
Tablet Weight		60	100

7.2 Calculation for volume of water required:

The main aim of the experiment is to optimize the water, in this the water is taken in different percentages for different formulations on the basis of weight of the tablet by using the following formula.

$$\text{Calculation for volume of water required} = \frac{\%\text{ of water up taken}}{100} * \text{weight of the tablet.}$$

Table 7.2: Composition of Zolpidem Tartrate with % of water uptakes of different formulations:

S. no	Ingredients (mg/tablet)	Formulations Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Zolpidem Tartrate	5	5	5	5	5	5	5	5	5
2	Lactose monohydrate	43.8	43.8	43.8	43.8	43.8	43.8	43.8	43.8	43.8
3	Microcrystalline cellulose	10	10	10	10	10	10	10	10	10
4	Sodium starch glycolate	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60
5	Purified water (%)	1%	2%	3%	4%	5%	6%	7%	8%	9%
6	Magnesium stearate	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60

Table7.3: Volume of water uptakes for single unit of different formulations:

S. no	Formulation	Unit weight(mg)	Water uptakes (ml)
1	F1	60	0.0006
2	F2	60	0.0012
3	F3	60	0.0018
4	F4	60	0.0024
5	F5	60	0.0030
6	F6	60	0.0036
7	F7	60	0.0042
8	F8	60	0.0048
9	F9	60	0.0054

7.3 Method of processing of Zolpidem Tartrate granules:

Table 7.4: Method of processing of Zolpidem Tartrate granules

S. no	Steps	Method of processing of granules
1	**Sifting:**	1.1) Lactose monohydrate (Pharmatose 200) is sifted through mesh #40. 1.2) Zolpidem Tartrate is sifted through mesh #30 1.3) Then Zolpidem Tartrate is co-sifted along with its equal quantity of lactose through mesh #40 1.4) Above blend 1.3 is co-sifted with its equal quantity of lactose through mesh #40. 1.5) Above blend 1.4 is co-sifted with remaining quantity of lactose through mesh #40. 1.6) Sodium starch glycolate is sifted through mesh #40.
2	**Dry mixing:**	Dry mixing has done with Zolpidem Tartrate, lactose monohydrate and sodium starch glycolate for 10 minutes
3	**Granulation:**	
	Binder addition:	Binder added to the dry mix over a period of 1-2 minutes with mixing.
	Kneading:	Wet mass kneaded for 1 minute.
4.	**Sifting of extra**	Microcrystalline cellulose is sifted through mesh #40

	granular material:	and sift magnesium stearate through mesh #40.
	Pre-lubrication:	Add sifted microcrystalline cellulose to granular portion and blended for 5 minutes.
5.	**Lubrication:**	Pre-sifted magnesium stearate added to the pre-lubricated blend over a period and blended for 5 minutes.

7.4 Tablet Compression:

After evaluation of powder blend, compression of tablets was done with the 18 punch station (PACIFIC) compression machine using 5mm circular punch and embossed with "E" on one side and "78" on other side.

Temperature and Humidity is maintained within the limits of: 25±2°C and humidity at 55±5%Rh.

Load Zolpidem Tartrate final blend and set a weight of 60 mg fill weight and compress the tablets at an average weight of 60 mg per tablet.

EVALUATION OF Tablets....

8. EVALUATION OF TABLETS

- **Evaluation of tablets:**
  - **Physico-Chemical Properties of Tablets.**
    - Appearance.
    - Thickness and size.
    - Hardness.
    - Friability.
    - Weight variation.
    - Drug content.
  - ***In-vitro* Drug Release Studies.**
  - **Stability Studies.**

8.1 Physico-chemical properties of tablets:

8.1.1 Appearance: *(Leon Lachman, 1991, Gilbert S, 2007)*

The tablets were visually observed for any capping, chipping, sticking and lamination.

8.1.2 Thickness and size:

The thickness and size of tablet can vary with no change in weight due to difference in Density of granulation, the pressure applied to the tablets and speed of the tablet compression machine. The thickness of the tablets was determined using a Vernier caliper. Three tablets from each type of formulation were used and average values were calculated.

8.1.3 Hardness:

There is a certain requirement of hardness in tablets so as to withstand the mechanical shocks during handling, manufacturing, packaging and shipping. Hardness tester (Monsanto tester) was used to measure hardness of tablets. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be taken as a zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2.

8.1.4 Friability:

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for four minutes, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche friabilator which was

then operated for 100 revolutions. The tablets were then dedusted and reweighed. Percent friability (% F) was calculated as follows,

% Friability = (Initial weight - Final weight / Initial weight) x 100.

8.1.5 Weight Variation: *(Indian Pharmacopoeia, 2007)*

The weight variation test is done by taking 20 tablets randomly and they were weighed individually. The composite weight divided by 20, provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by % deviation allowed and none should deviate by more than twice its percentage.

Table 8.1: Specifications of % weight variation allowed in tablets as per Indian Pharmacopoeia.

Average Weight of Tablet	% Deviation allowed
80 mg or less	10
More than 80 mg but less that 250 mg	7.5
250 mg or more	5

8.1.6 Drug content:

20 tablets of Zolpidem Tartrate from each formulation were taken and amount of drug present in each tablet determined. Powdered tablet equivalent to 25 mg was taken in 25 ml volumetric flask add 10ml of water and sonicate to get clear solution make up the volume with water to get 1mg/ml solution. From this solution pipette out 0.1ml into a 10 ml volumetric flask and made up the volume with water to get 10µg/ml solution and absorbance of resultant solution was measured at 266nm, water used as blank.

8.2 *In-vitro* drug release studies:

8.2.1 *In-vitro* dissolution of tablets: *(www.nihs.go.jp/drug/Orange)*

Drug release studies were carried out by using USP dissolution type II apparatus. The tablets were tested for drug release about 30 minutes, 900ml of distilled water used as dissolution medium. 5ml of samples were withdrawn at the interval of 5, 10, 15 and 30 minutes. Diluted up to 10 ml with distilled water. The absorbances were measured at 266 nm. Using a double beam UV spectrophotometer to find out the amount drug release of Zolpidem Tartrate.

Table 8.2: Parameters for *In -Vitro* drug release

1	Apparatus	USP type II apparatus (Paddle type)
2	Temperature	37 $\pm$ 0.5° C
3	Initial Volume	900ml
4	Speed	50 rpm
5	Drawn volume	5 ml
6	Running time	30 minutes in Distilled water
7	Absorbance	266 nm

8.3 Stability studies: *(Rhode C. T, Janes T. Garnsten, 2000)*

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled “Stability testing

of New Drug Substances and Products" describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

Stability studies were carried out at 40°C / 75% RH for the optimized formulation for 3 months. The micropellets were stored at 40°C/75% RH in closed high density polyethylene bottles for 3 months. The samples were withdrawn after periods of 1, 2 and 3 months. The samples were analyzed for its drug content and *In-vitro* drug release.

RESULTS & DISCUSSION....

9. RESULTS AND DISCUSSION

9.1 characterization of drug:

9.1.1 Colour and appearance:

The drug (Zolpidem Tartrate) colour is "White or half white Powder" as same as the reported reference.

9.1.2 Melting point:

The Melting point of Zolpidem Tartrate was found to be 218^0C ± 2.081. The reported melting point of Zolpidem is 216-222^0C. Hence, observed values are complies with USP.

9.1.3 Solubility study:

The Solubility of Zolpidem Tartrate in different solvents is given below:

Table 9.1: Solubility of Zolpidem Tartrate in different solvents

S. no	Solvent	Inference
1	Distilled water	Soluble.
2	Methanol	Sparingly soluble.
3	Methylelene chloride	Practically insoluble

9.1.4 Identification of drug:

Identification of drug was performed by FT-IR spectroscopic method.

9.1.4.1 Fourier transform Infra-Red spectroscopy (FT-IR):

The IR spectrum of Zolpidem Tartrate is shown in figure 9.1

The interpretation of IR frequencies are shown in table 9.2

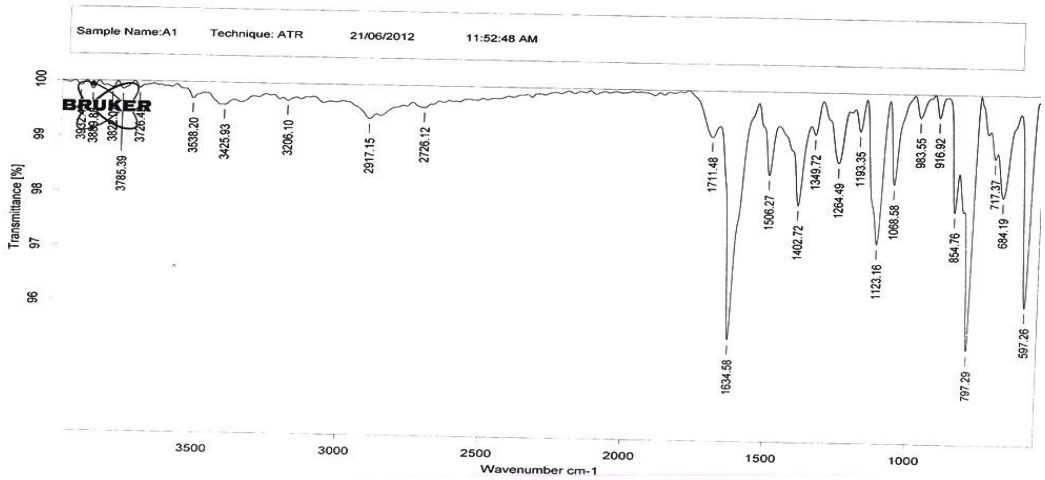


Figure 9.1: IR of Zolpidem Tartrate

Interpretation of FTIR spectrum:

Table 9.2 shows the peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to functional group of in Zolpidem Tartrate. Hence, the sample was confirmed as Zolpidem Tartrate.

Table 9.2: Characteristic frequencies in FTIR spectrum of Zolpidem Tartrate

Functional groups	Wave No. ($cm^{-1)}$
O-H Stretching	3785.39
C-H Stretching	3206.20
C=H Stretching	2762.12
N-H Cyclic Stretching	1711.48
C-O Stretching	1068.58
C-H Rocking	648.19

9.1.4 Spectroscopic studies of Zolpidem Tartrate:

9.1.4.1 UV Spectroscopy of Zolpidem Tartrate:

9.1.4.1.1 Determination of λmax and preparation of calibration curve of Zolpidem Tartrate by using distilled water:

UV absorption spectrum of Zolpidem Tartrate in distilled water shows λmax at 266 nm. Absorbance obtained for various concentrations of Zolpidem Tartrate in distilled water are given in Table 9.3. The graph of absorbance concentration for Zolpidem Tartrate was found to be linear in the concentration range of 2 – 20µg /ml. The drug obeys Beer- Lambert's law in the range of 2 – 20µg /ml.

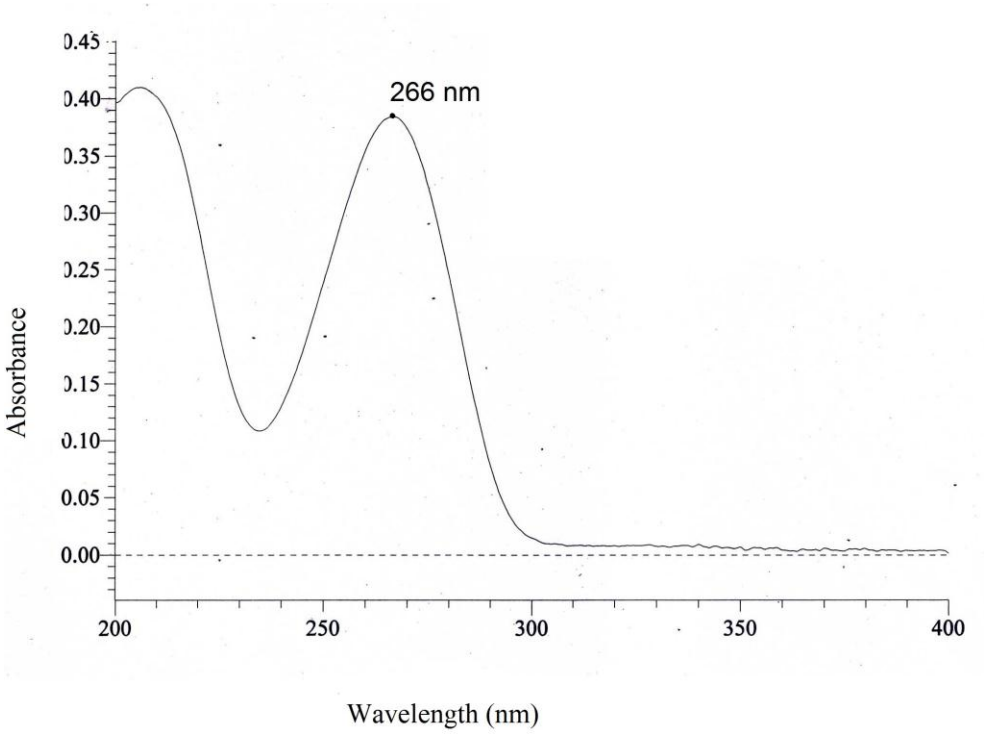


Fig. 9.2: Absorption maximum of Zolpidem Tartrate in distilled water

Table 9.3: Concentration and absorbance data for calibration curve of Zolpidem Tartrate in distilled water:

S. no	Concentration(µg/ml)	Absorbence
1	0	0.000
2	2	0.077
3	4	0.154
4	6	0.234
5	8	0.308
6	10	0.390
7	12	0.460
8	14	0.538
9	16	0.620
10	18	0.691
11	20	0.760

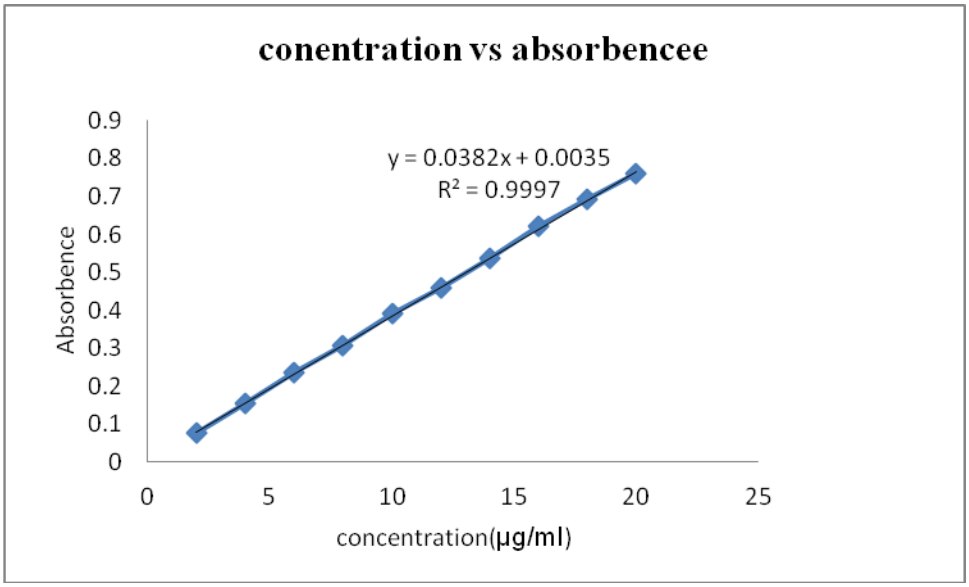


Figure 9.3: Calibration Curve of Zolpidem Tartrate in distilled water

The values of Correlation coefficient (R), Slope, Intercept obtained from the calibration curve are given in the Table 9.4.

Table 9.4: Data for Calibration Curve parameters of Zolpidem Tartrate in distilled water

S. no	Parameters	Values
1	Slope	0.0382
2	Intercept	0.0035
3	Correlation coefficient (R)	0.9997

9.1.5 Loss on drying:

The percentage loss on drying after 5 hours was found to be 0.897%. The sample passes test for loss on drying as per the limits specified in USP. (NMT 1%).

9.2 Drug - excipients compatibility studies:

9.2.1 Differential scanning calorimetry (DSC):

X: Zolpidem Tartrate

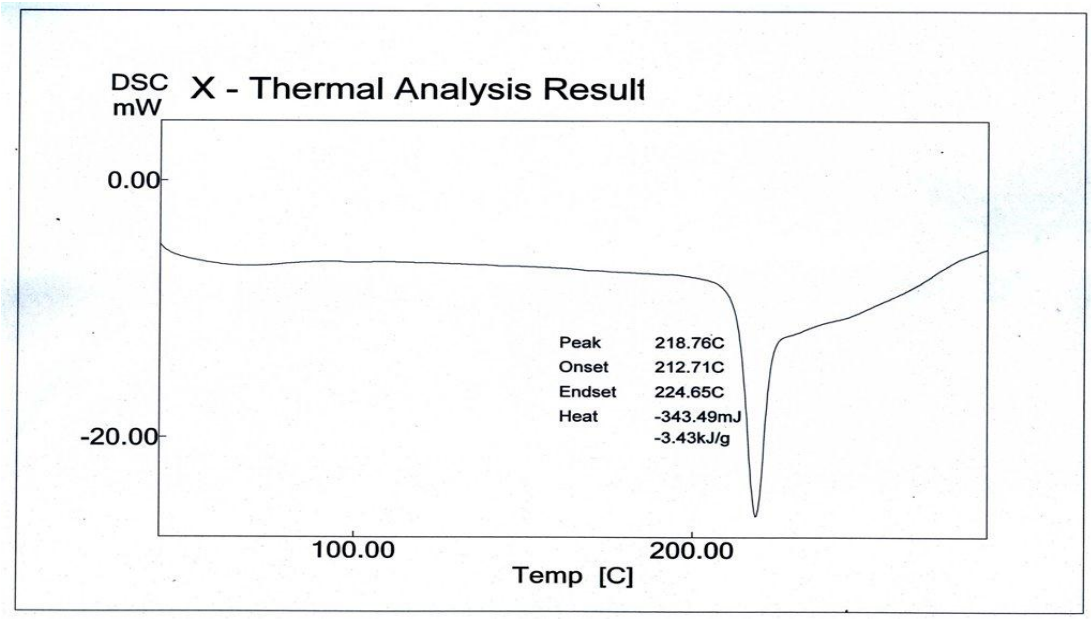


Figure 9.4: DSC Thermogram of Zolpidem Tartrate

X1: Excipients

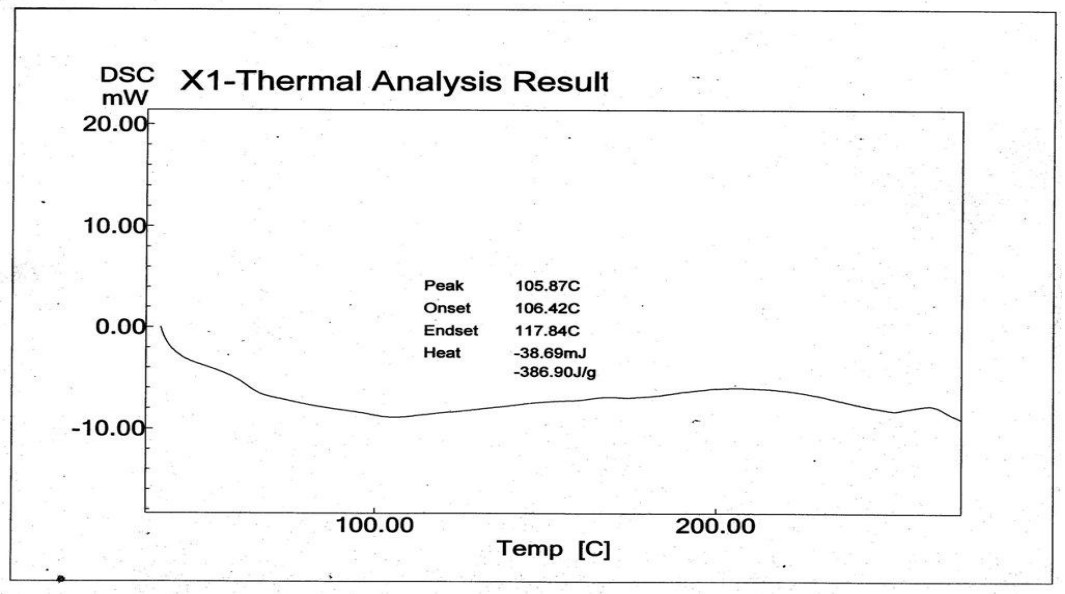


Figure 9.5: DSC Thermogram of excipients

X2: Zolpidem Tartrate + Excipients.

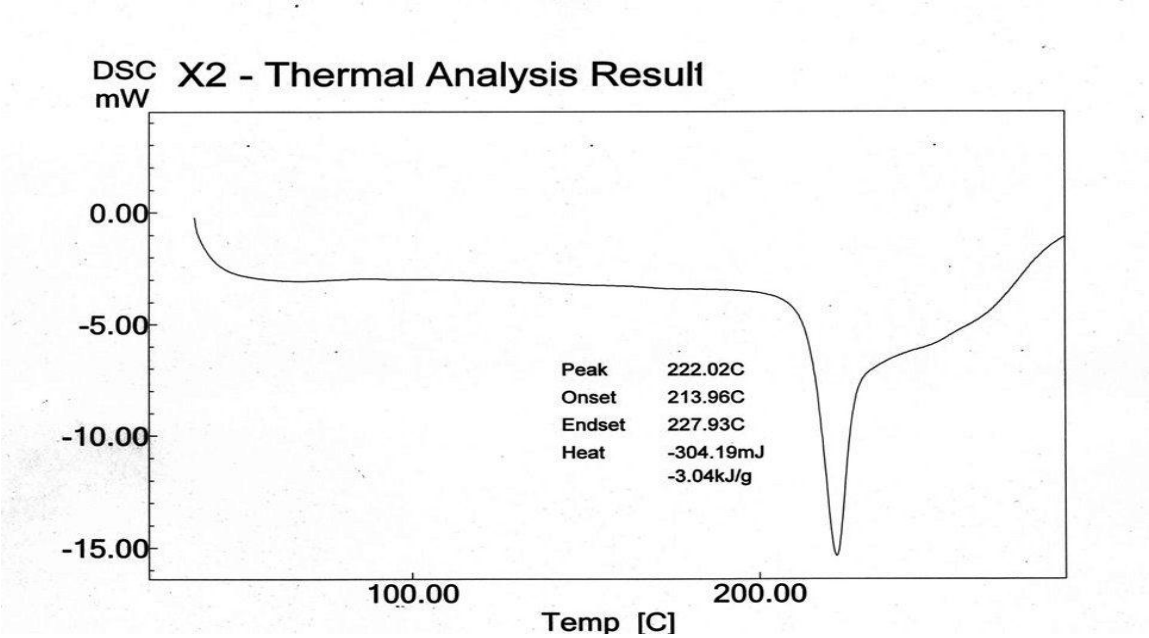


Figure 9.6: DSC Thermogram of Zolpidem Tartrate + Excipients

The results of DSC studies are given in above figure 9.4, 9.5 and 9.5. Pure Zolpidem Tartrate showed sharp endotherm at 218°C corresponding to its melting point. There was no appreciable change in the melting endotherms of Zolpidem Tartrate, Zolpidem Tartrate with excipients as compared to the thermo gram of Zolpidem Tartrate. So, it could be concluded that there is no interaction between Zolpidem Tartrate and Excipients used in the formulations.

9.3 Evaluation of Micromeritic properties of granules:

Table 9.5: Micromeritic properties of granules

Formulations Code	Angle of Repose (θ) (^{o})	BD (gm/ml)	TBD (gm/ml)	Carr's Index (%)	Hausner's ratio
F1	34.23±0.02	0.601±0.01	0.781±0.01	24.0	1.30
F2	30.04±0.02	0.601±0.01	0.769±0.01	21.0	1.28
F3	26.48±0.04	0.601±0.03	0.730±0.04	18.0	1.21
F4	24.01±1.06	0.614±0.01	0.731±0.02	16.0	1.17
F5	22.07±0.19	0.611±0.01	0.710±0.03	14.0	1.16
F6	24.80±0.33	0.602± 0.03	0.732±0.06	17.8	1.21
F7	29.02±0.15	0.611±0.01	0.754±0.01	18.6	1.22
F8	33.32±0.15	0.614±0.04	0.760±0.03	21.0	1.27
F9	34.51±0.04	0.625±0.06	0.830±0.05	25.0	1.32

All the values are expressed as a mean ± SD., n = 3

9.3.1 Angle of repose:

The results for angle of repose are recorded in Table 9.5. Angle of repose ranged from 22.07 ± 0.19 to 34.51 ± 0.04. The flow properties of granules in all formulations exhibit as F4, F5 and F6 has excellent flow, F3, F7 has good flow and F1, F2, F8 and F9 has possible flow.

9.3.2 Bulk density and Tapped bulk density:

The results are shown in Table 9.5. The values of BD and TBD were found to be in the range from 0.601±0.01 to 0.625±0.06gm/ml and from 0.710±0.03 to 0.830±0.05gm/ml respectively. So, it shows that all formulations have good flow properties and pack ability.

9.3.3 Carr's Compressibility Index:

The results for Carr's Compressibility Index are recorded in Table 9.5. The Carr's Compressibility Index were in the ranged from 14 to 25 %. This indicates that the formulations of F4, F5 and F6 has good flow, F2, F3, F7 and F8 has fair flow and F9 has poor flow properties of granules.

9.3.4 Hausner's ratio:

The results were summarized in Table 9.5. The Hausner's ratio were found in the ranged from 1.16 to 1.32. So it indicates that the all formulations have good flow and moderate flow properties.

9.4 Evaluation of tablets:

9.4.1 Evaluation of Physico-chemical properties of tablets:

Table 9.6: Physico-Chemical Properties of Tablets:

Formulations Code	Thickness** (mm)	Weight variation (%)	Hardness** (kg/cm^2)	Friability* (%)	Drug Content* (%)
F1	2.57±0.048	1.2105	4.4±0.297	1.55±0.9	99.20±0.04
F2	2.61±0.052	1.0998	4.3±0.150	1.24±0.3	98.20±0.04
F3	2.60±0.127	0.8006	4.0±0.114	0.89±0.9	98.17±0.08
F4	2.55±0.106	0.6005	3.7±0.153	0.66±0.5	99.36±0.12
F5	2.65±0.148	0.5012	3.5±0.197	0.48±0.3	100.05±0.04
F6	2.67±0.109	0.6005	3.3±0.242	0. 57±0.3	99.32±0.09
F7	2.62±0.070	0.7007	3.4±0.376	0.98±0.5	98.32±0.05
F8	2.59±0.042	1.0009	3.2±0437	1.06±0.4	98.95±0.078
F9	2.57±0.048	1.1004	3.1±0.197	1.14±0.3	97.52±0.15

*****All the values are expressed as a mean ± SD., n = 3

****** All the values are expressed as a mean ± SD., n = 6.

9.4.1.1 Appearance:

The tablets were observed visually and F1, F2 had shows chipping, F8, F9 had shows sticking defects and F3, F4, F5, F6 and F7 did not shows any defects after punching.

9.4.1.2 Thickness:

The thickness of formulations ranged from 2.57 ± 0.127mm to 2.68 ± 0.04. The values are recorded in Table 9.6.

9.4.1.3 Weight Variation:

The percentage deviation from average tablet weight for all the formulations ranged from 1.2105 to 0.5012 %. The results are showed in Table 9.6. Hence F3, F4, F5, F6, and F7 formulations complied with the test for weight variation as per IP.

9.4.1.4 Hardness:

The results of Hardness of tablets were recorded in Table 9.6. It was found that the values are ranged from 3.15 ± 0.242 to 4.48 ± 0.676 kg/cm^2. Hardness values were satisfactory and indicated good mechanical strength of tablets.

9.4.1.5 Friability:

The Percentage Friability of all the formulations showed in Table 9.6. The results are ranged from 0.487±0.170 to 1.55693±0.299%. So, the percentage loss of Friability of the formulations F3, F4, F5, F6 and F7 was found to be less than 1 %.

9.4.1.6 Drug content:

Drug content was found to be uniform among different batches of tablets and ranged from 97.20±0.15 to 100.05 ± 0.07%. These results showed that the all formulations having percentage drug content within the specified limits as per USP.

9.5 *In-vitro* drug release studies:

9.5.1 *In-vitro* dissolution profile of tablets:

❖ **Dissolution profile for formulation F1, F2 and F3:**

Table 9.7: *In-vitro* dissolution data of Formulation F1, F2 and F3

S. no	Time(min)	Dissolution medium	% of cumulative drug release		
			F1	F2	F3
1	0	900ml of distilled water	0.0000	0.0000	0.0000
2	5		71.5371	76.0484	79.3651
3	10		78.5471	82.2081	87.1832
4	15		78.6545	89.3154	89.3154
5	30		95.9490	96.6502	98.0811

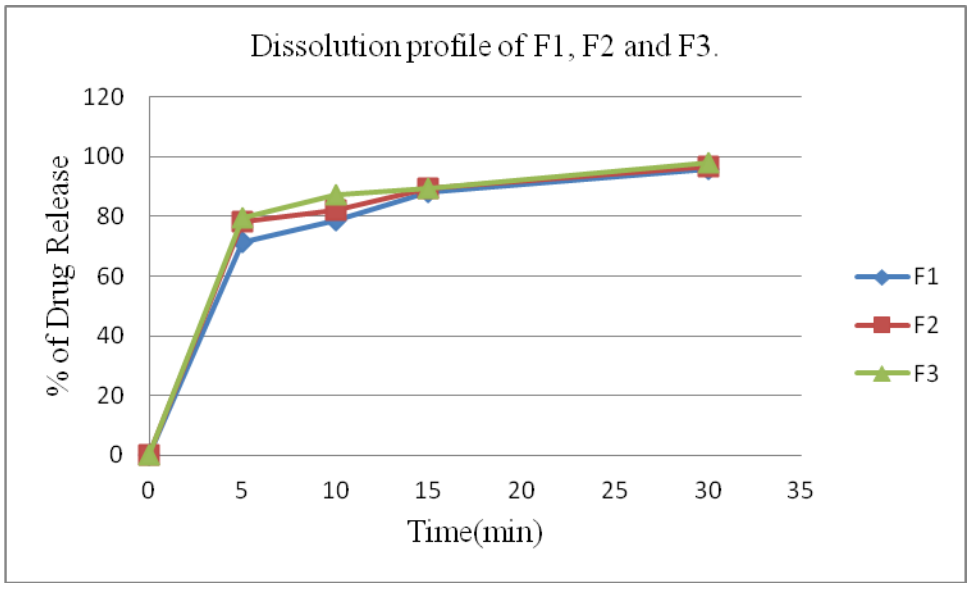


Figure 9.7: Cumulative percentage drug release profile of F1, F2 and F3.

❖ **Dissolution Profile of Formulation F4, F5 and F6:**

Table 9.8: *In-vitro* dissolution data of Formulation F4, F5 and F6.

S. no	Time(min)	Dissolution medium	% of cumulative drug release		
			F4	F5	F6
1	0	900ml of distilled water	0.0000	0.0000	0.0000
2	5		80.7660	82.4450	81.2604
3	10		88.8416	90.5000	92.8691
4	15		92.3952	94.2950	94.0536
5	30		99.0288	99.5026	98.5549

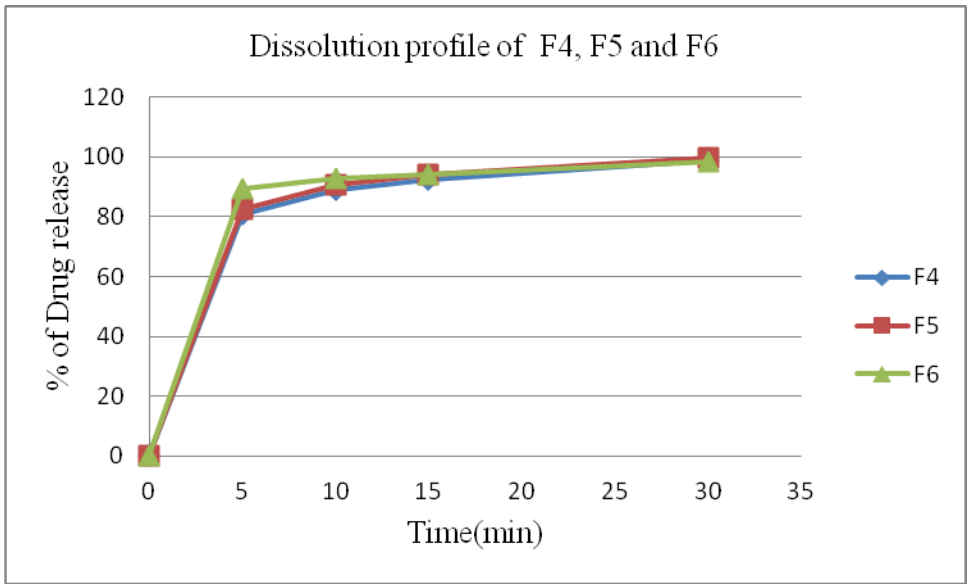


Figure 9.8: Cumulative percentage Drug release profile of F4, F5 and F6.

❖ **Dissolution Profile of Formulation F7, F8 and F9:**

Table 9.9: *In-vitro* dissolution data of Formulation F7, F8 and F9

S. no	Time(min)	Dissolution medium	% of cumulative drug release		
			F7	F8	F9
1	0	900ml of distilled water	0.0000	0.0000	0.0000
2	5		82.9188	83.1557	83.6295
3	10		92.8611	92.6322	94.0536
4	15		94.5276	94.5274	95.4751
5	30		98.0811	97.3704	96.8966

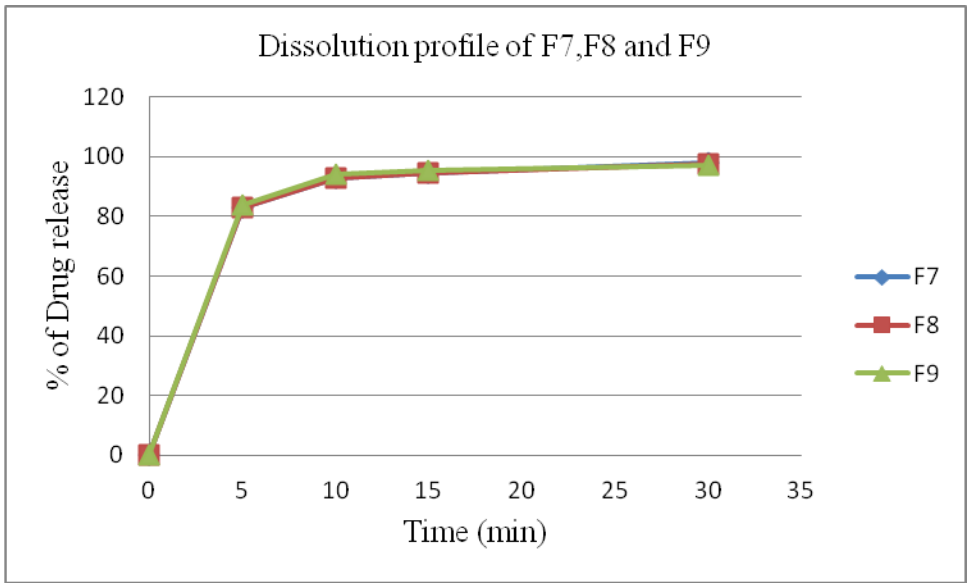


Figure 9.9: Cumulative percentage Drug release profile of F7, F8 and F9

Table 9.10: *In-vitro* dissolution data of Formulation F1 - F9

S.no	Time (min)	Dissolution medium	% of cumulative drug release								
			F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	900 ml of distilled water	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
2	5		71.5371	76.0484	79.3651	80.7660	82.4450	81.2604	82.9188	83.1557	83.6295
3	10		78.5471	82.2081	87.1832	88.8416	90.5000	92.8691	92.8611	92.6322	94.0536
4	15		78.6545	89.3154	89.3154	92.3952	94.2950	94.0536	94.5276	94.5274	95.4751
5	30		95.9490	96.6502	98.0811	99.0288	99.5026	98.5549	98.0811	97.3704	96.8966

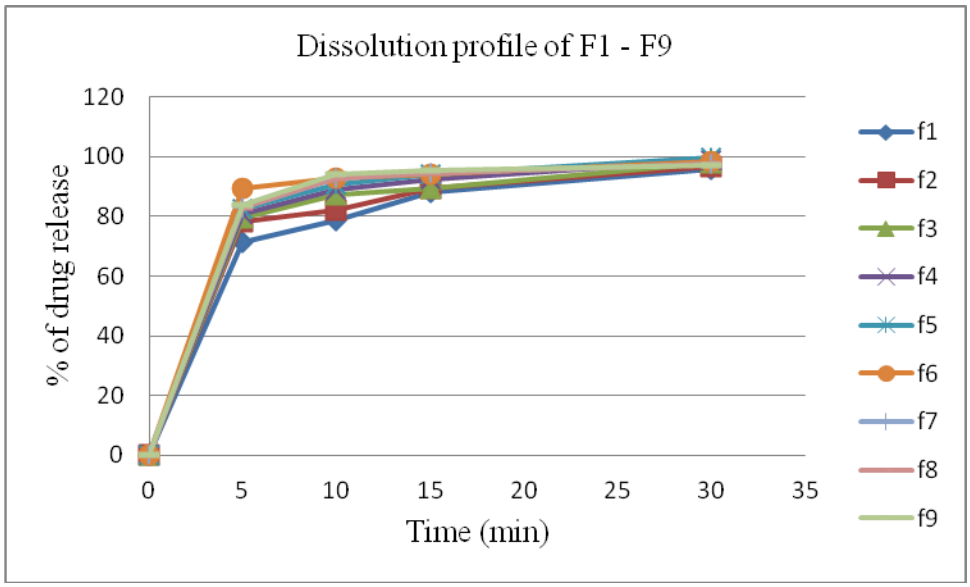


Figure 9.10: Cumulative % Drug release profile of formulation F1 – F9

In-vitro dissolution studies of all the formulation of Zolpidem Tartrate tablets were carried out in water. The study was performed for 30 minutes and cumulative drug release was calculated at different time interval**.**

The formulation F1, F2 and F3 showed the drug release 95.94, 96.65 and 98.08% for 30 mins, F4, F5 and F6 showed the drug release 99.02, 99.50 and 98.55% for 30 mins and F7, F8 and F9 showed the drug release 98.08, 97.37 and 96.89 for 30 mins. The drug released from formulation F5 was found to be 99.50% at the end of 30 mins, which is showing high percentage drug release. Hence F5 is considered as a best formulation.

9.6 Stability studies:

From the results it was found that formulation F5 is the best formulation amongst the 9 formulations. Thus formulation F5 was selected for stability studies.

9.6.1. Stability studies at the end of First month (30 days):

9.6.1.1. Hardness:

The hardness of tablet after one month of stability studies was studied. The results are within the limits. The data is shown in Table 9.11.

Table 9.11: Hardness of formulation F5 at the end of 1 month of stability

S. no	Formulation	Hardness (kg/cm^2)
1.	F5	3.5±0.08

All the values are expressed as a mean ± SD., n = 6

9.6.1.2 Drug content:

The Percentage drug content of tablet after one month of stability studies was studied. The results are within the official limits. The data is shown in Table 9.12.

Table 9.12: Drug content of formulation F5 at the end of 1 month of stability

S. no	Formulation	Percentage drug content
1.	F5	99.72±0.2

All the values are expressed as a mean ± SD., n = 3

9.6.1.3 *In-vitro* dissolution study:

The Cumulative percentage drug release from F5 tablet after one month of stability was studied. The data is shown in Table 9.13.

Table 9.13: *In-vitro* dissolution data of formulation F5 at the end of 1 month of stability

S. no	Time (min)	% of Cumulative drug release
1	0	0.0000
2	5	82.3450
3	10	90.4000
4	15	94.0950
5	30	99.4720

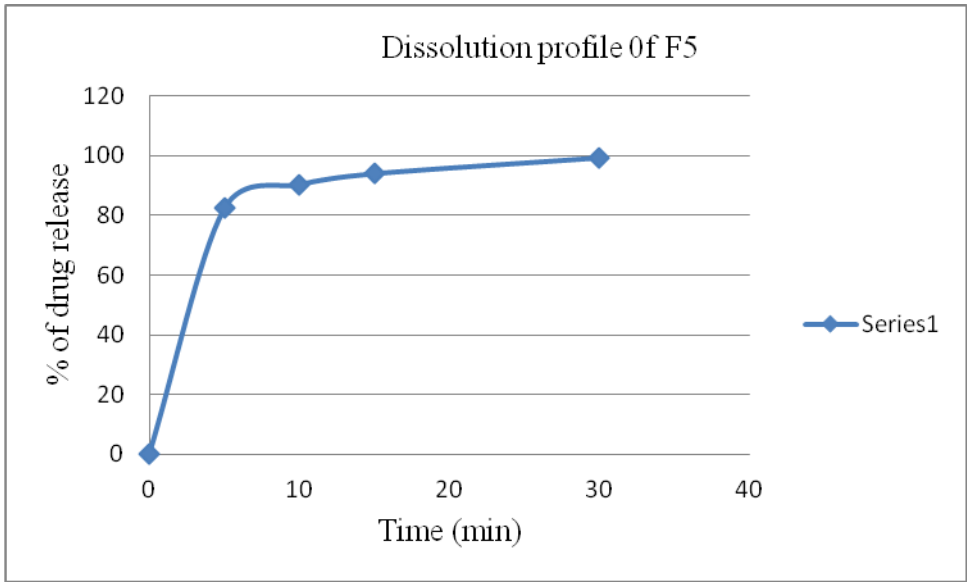


Figure 9.11: *In-vitro* dissolution profile of formulation F5 at the end of 1 month of stability

9.6.2. Stability studies at the end of Second month (60 days):

9.6.2.1. Hardness:

The hardness of tablet after Two months of stability studies was studied. The results are within the limits. The data is shown in Table 9.14.

Table 9.14: Hardness of formulation F5 at the end of 2 months of stability

S. no	Formulation	Hardness (kg/cm^2)
1.	F5	3.5± 0.03

All the values are expressed as a mean ± SD., n = 6

9.6.2.2 Drug content:

The Percentage drug content of tablet after Two months of stability studies was studied. The results are within the official limits. The data is shown in Table 9.15.

Table 9.15: Drug content of formulation F5 at the end of 2 months of stability

S. no	Formulation	Percentage drug content
1.	F5	99.57±0.2

All the values are expressed as a mean ± SD., n = 3

9.6.2.3 *In-vitro* dissolution study:

The Cumulative percentage drug release from F5 tablet after Two months of stability was studied. The data is shown in Table 9.16.

Table 9.16: *In-vitro* dissolution data of formulation F5 at the end of 2 months of stability

S. no	Time (min)	% of Cumulative drug release
1	0	0.0000
2	5	82.3050
3	10	90.3700
4	15	94.0550
5	30	99.4415

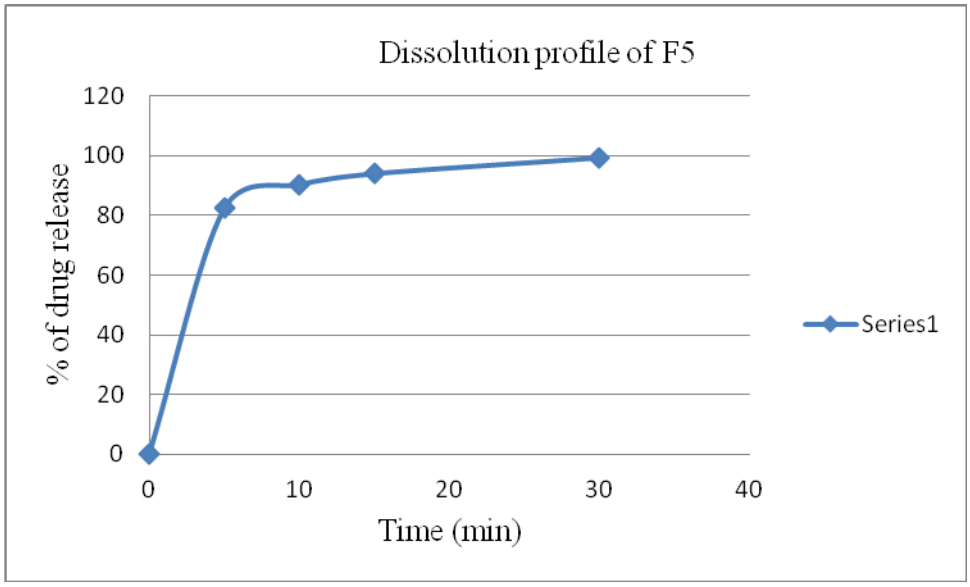


Figure 9.12: *In-vitro* dissolution profile of formulation F5 at the end of 2 months of stability

9.6.3 Stability studies at the end of Third month (90 days):

9.6.3.1 Hardness:

The hardness of tablet after Third months of stability studies was studied. The results are within the limits. The data is shown in Table 9.17.

Table 9.17: Hardness of formulation F5 at the end of 3 months of stability

S. no	Formulation	Hardness (kg/cm^2)
1.	F5	3.5±0.01

All the values are expressed as a mean ± SD., n = 6

9.6.3.2 Drug content:

The percentage drug content of tablet after Third month of stability studies was studied. The results are within the official limits. The data is shown in Table 9.18.

Table 9.18: Drug content of formulation F5 at the end of 3 months of stability

S. no	Formulation	Percentage drug content
1.	F5	99.45 ±0.13

All the values are expressed as a mean ± SD., n = 3

9.6.3.3 *In-vitro* dissolution study:

The Cumulative percentage drug release from F5 tablet after Two months of stability was studied. The data is shown in Table 9.19.

Table 9.19: *In-vitro* dissolution data of formulation F5 at the end of 3 months of stability

S. no	Time (min)	% of Cumulative drug release
1	0	0.0000
2	5	82.2850
3	10	90.3300
4	15	94.0150
5	30	99.3937

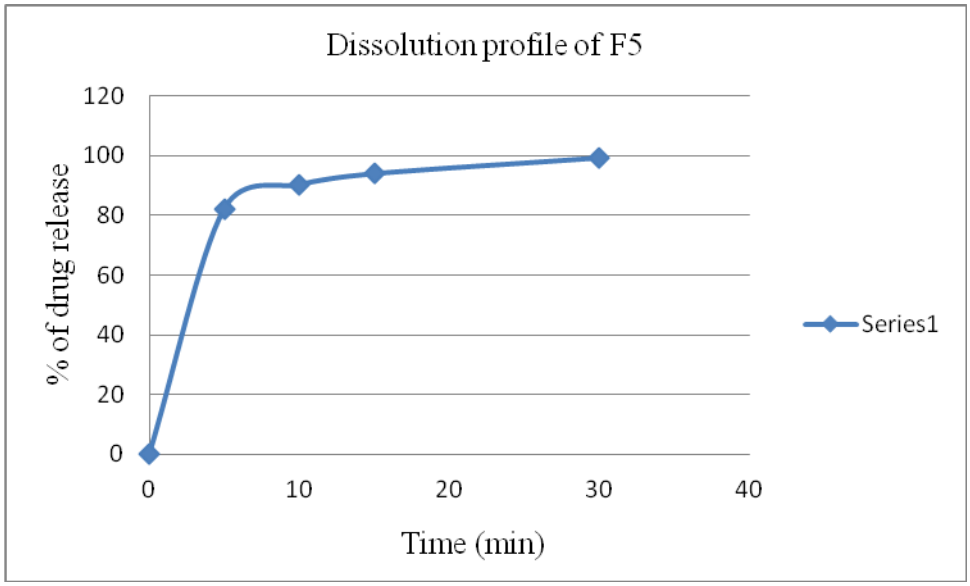


Figure 9.13: *In-vitro* dissolution profile of formulation F5 at the end of 3 months of stability

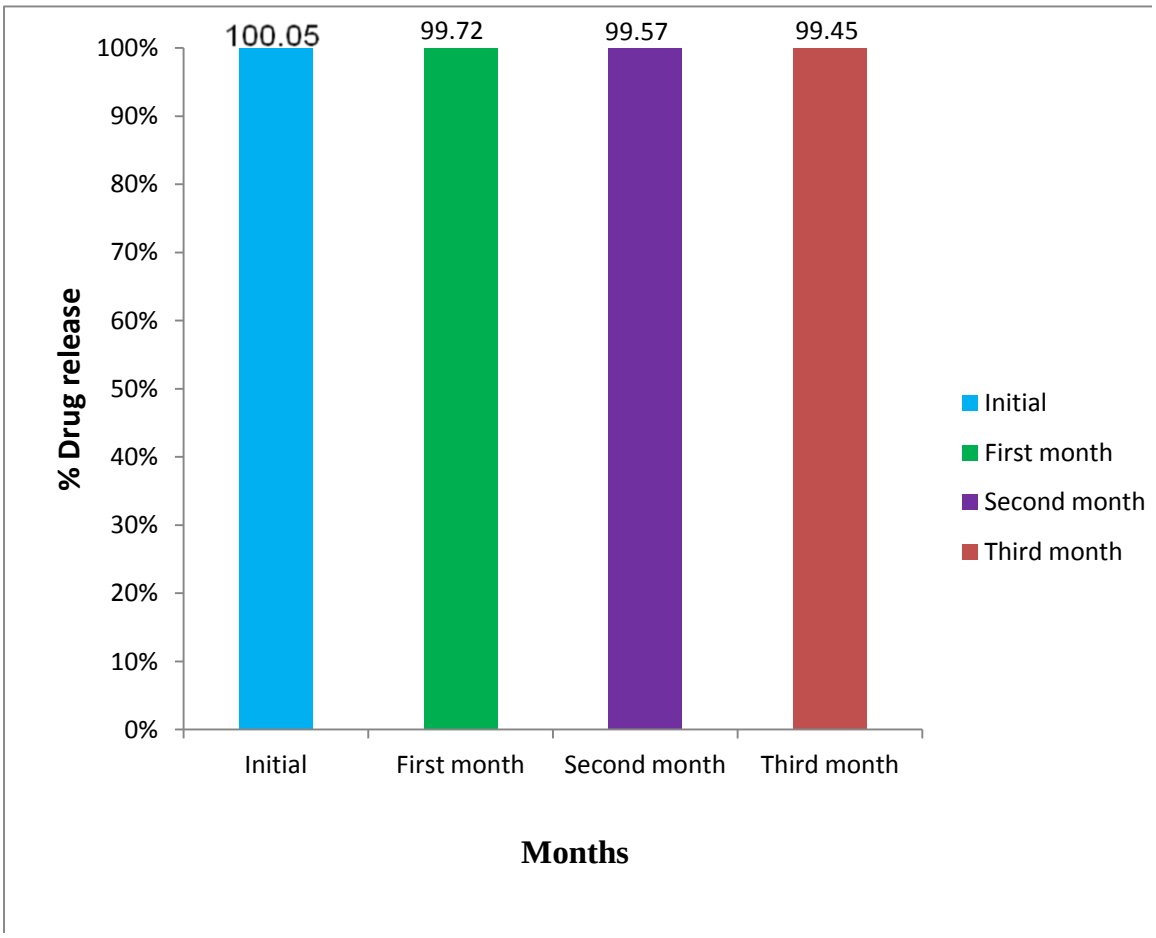


Figure 9.14: Comparisons of % drug content for formulation F5 with initial and different periods of stability

No statistically significant differences were observed in percentage drug content and cumulative percentage drug release in optimized formulation at the end of three months of stability studies.

So it can be concluded that the formulation is stable for short term storage conditions.

SUMMARY & CONCLUSION....

10. SUMMARY AND CONCLUSION

The process development and optimization of Zolpidem Tartrate tablets by moisture activated dry granulation (MADG) technique was performed in the present study. The process development and optimization Zolpidem Tartrate tablets were performed by using different percentages (%) of water in all the formulations.

Preformulation study was carried out for powder blends, it was evaluated to determine the flow characteristics by angle of repose, bulk density, tapped density, carr's index and hausner's ratio. The data obtained from these studies indicated that the powder blends some had good flow, some had moderate flow properties.

The tablets were prepared using with different percentages of water by Moisture activated dry granulation technique. The formulated tablets were evaluated for physical characterization like thickness, hardness, friability, weight variation and drug content. All the physical parameters of prepared tablets compiles with and without IP specifications.

Evaluation studies of all formulations showed that the drug content, weight variation and friability as per the standards given in IP. The hardness of all formulations was within the limits.

The *in-vitro* dissolution studies closely indicate that among nine formulations the formulation F5 was found to be the best with high percentage of drug release (99.50%).

From the stability data, it can be concluded that there was no significant changes in any parameters. Hence the formulation F5 is considered to be highly stable formulation.

The overall studies indicate that 5% of water up taken showed satisfactory properties. Among the nine formulations the formulation F5 exhibited optimum drug release profile.

Hence, it is concluded that the formulation F5 will be best formulation.

FUTURE PROSPECTS....

11. FUTURE PROSPECTS

In the present work Zolpidem Tartrate tablets were formulated by Moisture activated dry granulation (MADG) technique.

In this work only Physico-chemical characterization and *in-vitro* evaluation of Zolpidem Tartrate were done.

1. Along with *in-vitro* release study *in-vivo* release studies are also important. So in future *in-vivo* release study using different models are required to set the *in-vitro in-vivo* correlation which is necessary for development of successful formulation and also long term stability studies are necessary.
2. Study the effect of various geometric shapes, in a more excessive manner than previous studies, extended dimensions.

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